KISTER

THE LIVING UNIVERSE

An Encyclopaedia of
the Biological Sciences

# The human machine
## *adjustments*

# THE LIVING UNIVERSE

## An Encyclopaedia of the Biological Sciences

*With an introduction*
*by M. F. Perutz, CBE, FRS,*
*Nobel Laureate in Chemistry*

Biology is the science of life—that branch of the sciences which touches everyone most nearly. In the past ten years more striking developments in biological research have taken place than at any other period. The breakthrough which is the key to so much of this work was the discovery in 1953 of the structure attributed to DNA — deoxyribonucleic acid — the chemical basis of the genes which is responsible for the handing down of hereditary characteristics. As a result recent discoveries in biology have been most important and prolific.

Now these momentous discoveries about man and the world he lives in have been collected in eight volumes which will rank among the most important scientific publications of the post-war years. 250 experts from many countries, among them two Nobel Prizewinners, have collaborated to describe the entire range of modern biological and medical research and every manifestation of living matter has been included. The result is a fascinating work, which makes this knowledge available in concise form to the general reader, as well as to scientists in other disciplines.

The unique quality of this publication lies in the combination of some 2,000 magnificent illustrations, 1,500 of them in full colour, with lucidly written texts of the very highest authority. Ranging from the simplest cells to the complexity of man, *The Living Universe* is an exploration in depth of the entire spectrum of life on earth and an introduction to the transformation of man in the world of tomorrow.

Dr. M. F. Perutz writes in his introduction:

**'Modern biology has become more like physics, and its new face is reflected in these volumes. Throughout, the emphasis is on the experimental approach rather than on pure observations. Solutions to the great outstanding problems of medicine may well come, not only through a study of man, but also through ingenious experimentation on some lowly species. This encyclopaedia introduces the reader to some of the exciting discoveries made in studies of viruses and unicellular organisms.'**

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# THE LIVING UNIVERSE
## *An Encyclopaedia of the Biological Sciences*

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# The human machine

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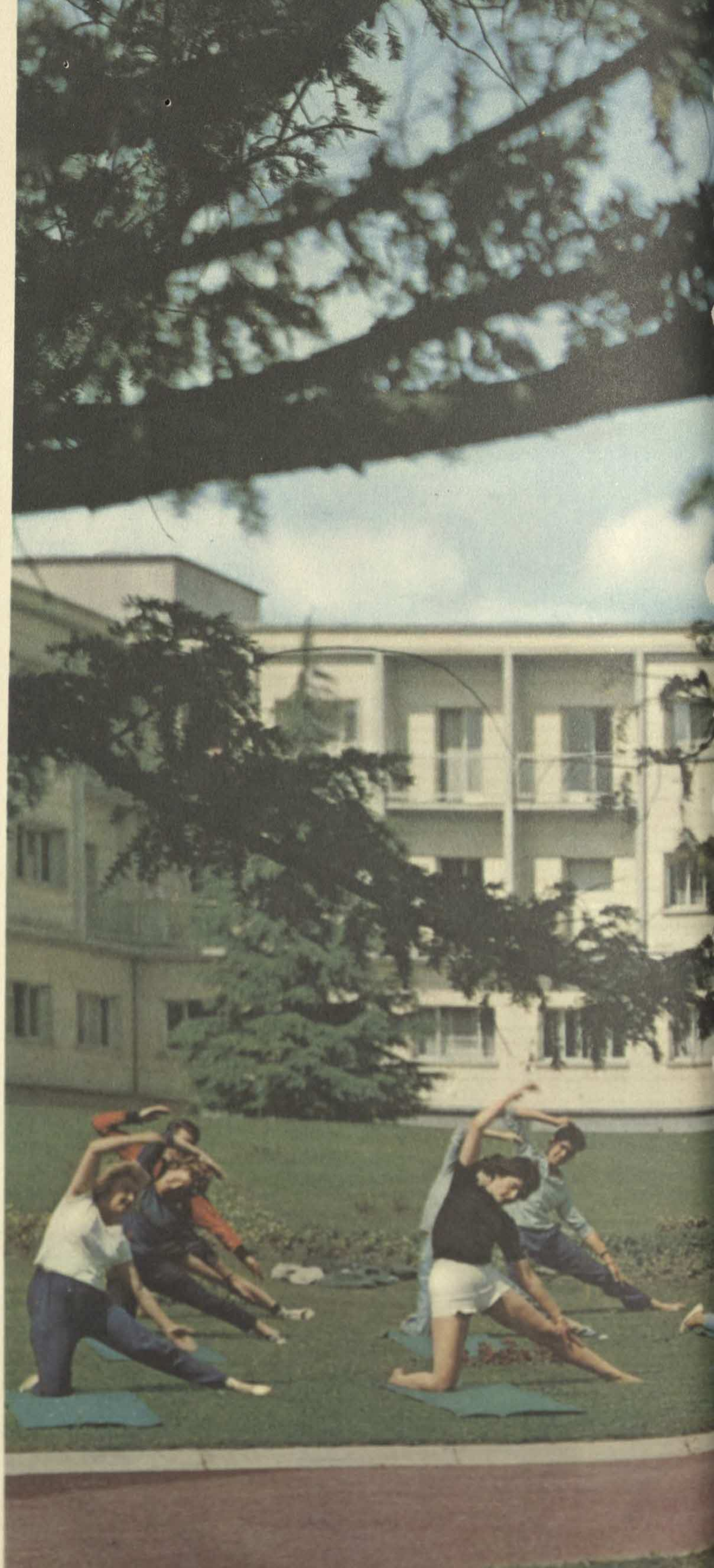
*In the modern conception of medicine, treatment does not consist only of applying prescriptions or administering remedies, but also of carefully readjusting the displaced cogwheels of the human machine. There are several ways of doing this: by chemical action, by physiological compensation, by psychological adjustment, and by influencing the environment. The reconditioning of the individual is, in fact, a cardinal feature of the cure. Thus, after actual treatment, physical and mental rehabilitation of the patient constitutes a thorough and effective adjustment of the disordered organism.*

*This illustration shows rehabilitation treatment in healthy and pleasant surroundings at the Maison-Lafitte Centre, near Paris, for the after-care of tuberculous patients.*



# THE LIVING UNIVERSE
## *An Encyclopaedia of the Biological Sciences*

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# The human machine: *adjustments*

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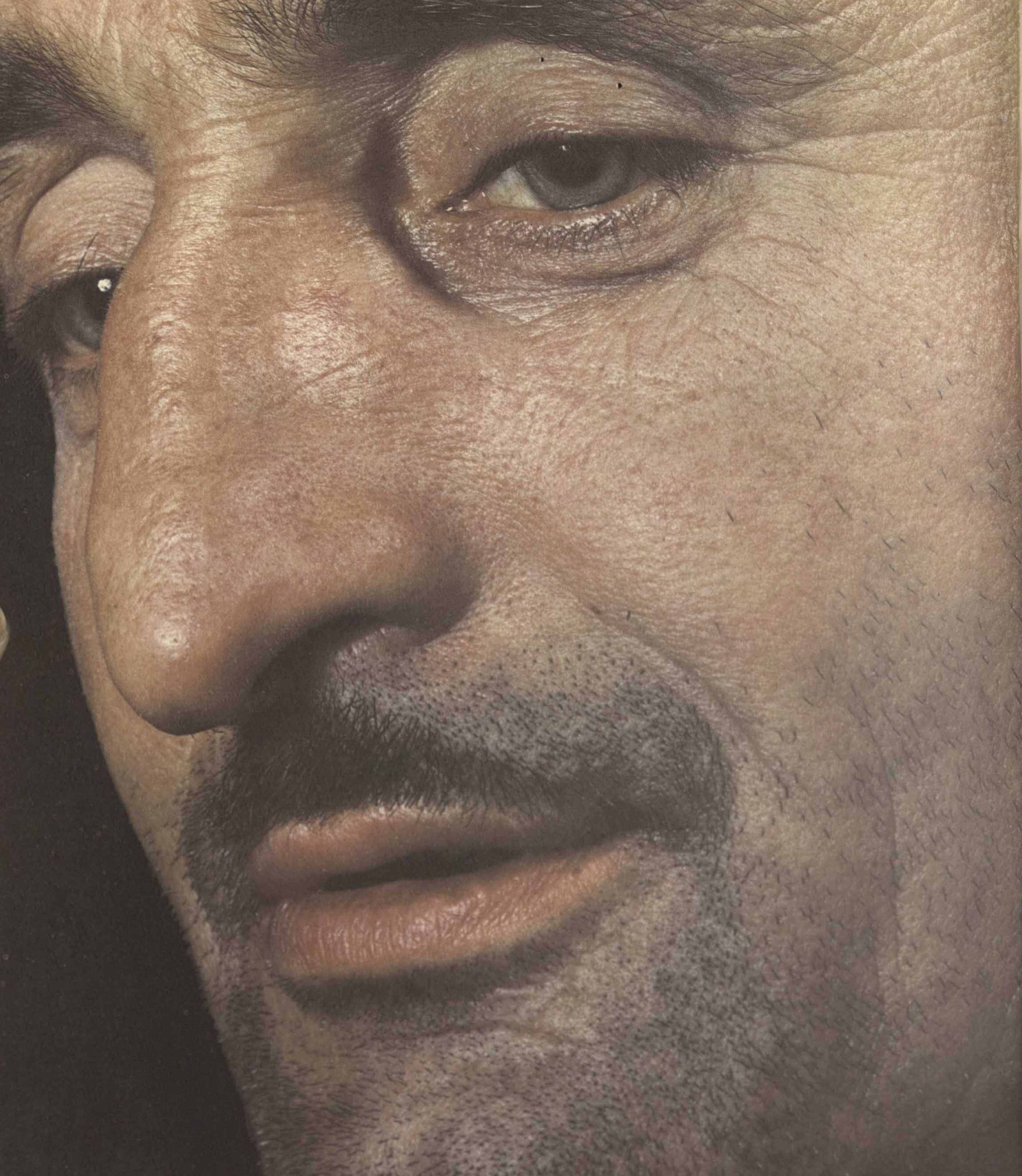
*The illustrations have been prepared under the supervision of Professor Raoul Kourilsky*



# The science of the patient

*Raoul KOURILSKY*

In relation to the biology of disease, medicine is an applied science. But as it deals with man, it cannot be considered a mere appendix or a sort of prolongation of biology. It has its own place among the sciences of the human being; it is the science of man as a patient, the science of the sick person. Medicine has already supplied us with far-reaching knowledge of normal man and will supply more and more in the future. This helps us to understand his personality, to predict his reactions, and to discern the psychological repercussions of disease.

For while disease disturbs man's physiology, it also creates in him a psychological conflict. Any unexpected disorder interrupts his ordinary activities and so makes him aware of his body. As long as the disorder continues, there is a different person inside him, against whom he reacts with all his emotional resources. He is no longer a free man.

## *The drama of the patient*

The marvellous regulatory mechanism which, in a healthy person, maintains the constancy of the internal environment, so that all the cells may live under proper conditions, ensures the autonomy of the physique in relation to the changing influences of its external environment. This system of adjustment allows man to unfold the full range of his possibilities without being entirely subject to external conditions. But this freedom, which derives from a strict internal determinism, is not absolute. It operates within the limits of the physiological possibilities of the body and under its environmental conditions: but when the body has adapted itself to its external environment and the regulation of the internal environment has been secured, man is then free to make use of his powers of action. This freedom is perceived psychologically: man is informed of his bodily resources and this gives him an impression of physical freedom.

If the regulatory functions of the body are impaired, so that man is informed by some symptom of a change in his condition, then this impression of freedom ceases: his psychological autonomy is impaired.

The slightest illness emphasizes all the problems of his life. It impairs his relationships with his external environment (work, profession and family) and disturbs the plans that he must make for his life, and which he must continually readjust in order to go on living.

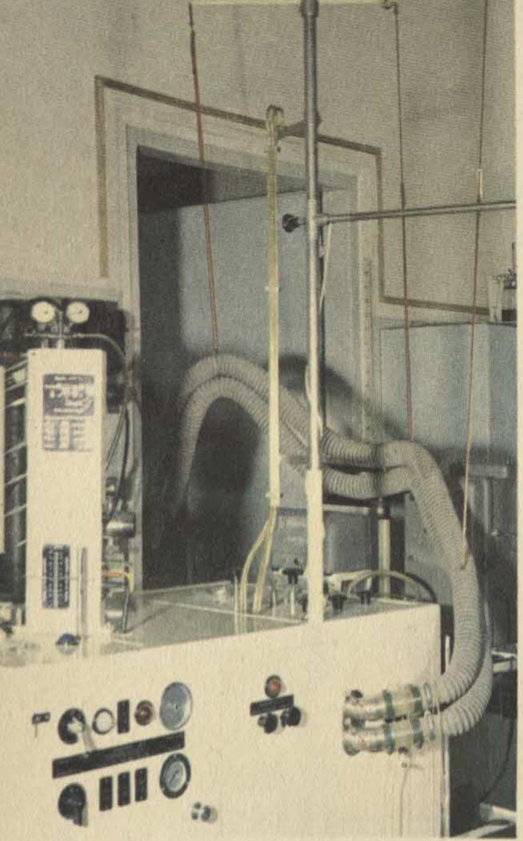
Such is the relationship between our psychological and physiological activities that co-operation between them is essential to life. Man lives only because he wants to live, because he wants to make use of all his vital faculties, based on his own capacities and his ability to influence his environment. If he no longer has the will to live, he dies. The nervous spur occasioned by interaction of the phenomena of life ceases; psychological and neurobiological adjustments become anarchic and the gravest organic consequences ensue.

Some asthmatics die because, during periods of great distress, they feel unable to live. Others, when they feel incapable of coping with life and fall victims to infectious diseases, are especially threatened, and, until antibiotics were discovered, they almost always fell ill and died.

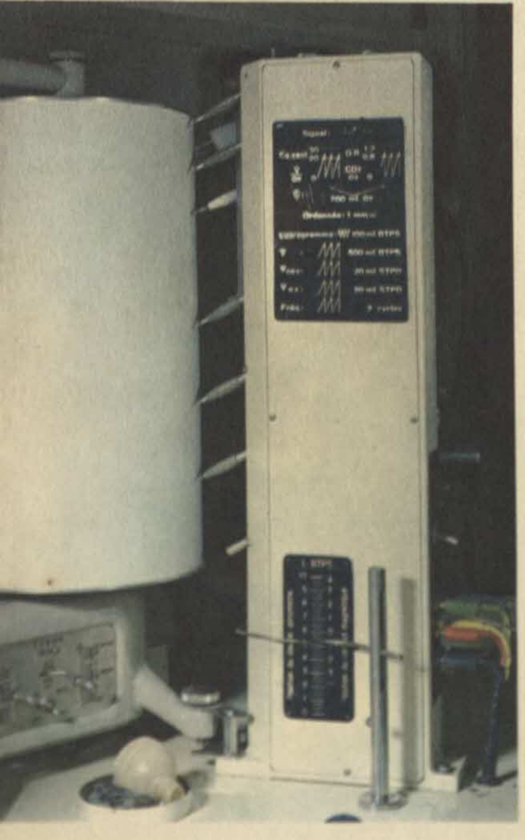
Of course, illness does not necessarily lead to situations as dramatic as this, but however slight it may be, illness undermines self-composure and creates distress. It is because each person dreads the difficulties of this situation that he passionately desires to be helped, not only physically, but also psychologically. He expects not only sympathy from his doctor, but feels a profound need to be guided and reconciled with himself. The doctor must know that it is possible to influence the regulatory functions of the body radically by acting on the emotional psychology of the patient, not haphazardly but by deliberate study of the make-up of his personality. He should not consider the organic changes that he finds by this means as coincident or sporadic factors, but as results of an action that has affected mechanisms of extreme precision. In short, the doctor's duty is that of thoroughly understanding the patient and working with him and through him in all that has to be accomplished.

This attitude is very different from earlier conceptions of the doctor's role, which consisted in his curing the disease without attempting to understand the patient's personality. The change is fundamental. It is now possible only because progress in the biological study of disease has given the doctor considerable knowledge of the phenomena and mechanisms of the body which enable him not only to recognize and correct them, but also to enlist the patient's help in his understanding of the

*Disease often shows itself by apprehension which undermines the patient's equanimity and creates distress; the sequelae of such a condition as duodenal ulcer are very characteristic in this respect (see the photograph on the left). The doctor must give moral support and advice in order to prepare the patient for the possibility of drastic treatment, such as, in this case, gastrectomy. (Photo Lod).*



*The doctor today is a kind of engineer; he cannot work without the help of numerous and complex forms of apparatus. (Above) Fleisch's metabograph. (Below) the kymograph, part of the metabograph. (Photo Lod).*



patient's physiological reactions by revealing a large number of reliable and verifiable facts.

But in order to do this the doctor must have a full knowledge of his subject and must be proficient in the technique essential for the diagnosis of diseases or disorders; and he must learn how to cure them both. It is clear, however, that one man alone cannot successfully carry out such a task. He will succeed in it only by co-operation between all who are involved. As in all scientific activities, and especially in biology, team-work is essential. The composition of the team varies according to the nature of the problem—medical or surgical.

The human organism requires extremely precise adjustments if it is to bring all its possibilities freely into play. Even long-approved scientific methods, if inappropriately applied, are not only incapable of reversing the course of a disease but may even threaten the regulatory mechanisms that are still working normally. In both surgery and medicine the best results can be got only by perfectly planned co-operation on both the biological and the psychological plane, which presupposes adequate proficiency in this two-fold approach by all concerned.

## *Scientific investigation of the patient*

It is still not usual to regard clinical medicine (that is to say, studies made at the patient's bedside) and therapeutic medicine (the treatment of the disease) as scientific activities. But we must not be disquieted by a word. The science of man does not scorn the respect that one owes to man; on the contrary, the necessity for a profound knowledge of the psychology of the patient, and the respect with which his physiological regulatory mechanisms must be studied and corrected, are factors just as important as the sympathy which is traditionally given to the patient by the doctor. Far from excluding this sympathy, these factors incorporate it in much more effective action, which must be pursued throughout the long and difficult processes of investigation and treatment.

It is essential that this investigation and treatment should be conducted with rigorous scientific discipline. But discipline does not mean automatism; it does not mean the blind application of formulae. Knowledge of regulatory functions, and the obligation to rectify them, exclude theoretical deduction. They postulate a high degree of adaptability—of the mind, the emotions, and the senses, and a subordination in principle to the physiological mechanisms and the personality of the patient.

Man has thus nothing to fear from a thorough scientific investigation; on the contrary, in the light of the triumphant progress of biology, such a procedure is an indispensable safeguard. It is by the precise application of biological data that the doctor can protect and cure. Science offers no dangers to the patient; but insufficient knowledge, a return to the routine of empiricism, ignorance, and contempt for the regulatory mechanisms of the body, may easily be dangerous. What is true for surgery is also true for medicine.

## *Clinical examination*

The first thing for the doctor and the patient to do together is to reconstruct the history of the illness. This is a long and often difficult undertaking if the patient's memory is unreliable. It is always necessary to allow time for the association of ideas to crystallize round definite events and professional and family circumstances. The amount of information that can be collected in this way is often so great that the disease can be recognized in all its details, and in seventy per cent of cases a valid hypothesis on its nature and origin can be formulated.

Contrary to what is often thought, the least of the sensations described by the patient are of great importance: none of them is without significance and all of them must be carefully noted. At the first interview the doctor can assess the patient's personality and the patient can learn about his illness.

The second phase of the investigation consists in noting and assessing those symptoms that the patient has not mentioned, by undertaking a thorough and general examination of him. At this stage the doctor must turn himself into a recording instrument of the utmost sensitivity, exercising his five senses with virtuosity and intelligence and allowing nothing to escape him.

As soon as the results of the examination are compared with those obtained by questioning the patient, it is possible to tell whether the initial hypothesis is valid or whether it must be changed. It is often necessary to consider several hypotheses, to assign to each a coefficient of probability, and then to eliminate all the invalid hypotheses by differential appraisal. The interrogation and examination of the patient and the rational discussion of the data require a considerable mental effort.

Inaccuracy increases with speed. The proportion of mistakes increases if the doctor has to examine many patients in a short time. The intuition which some scientists show in mathematics or physics does not obtain in biology or in medicine, because these disciplines bring into play a number of very important mechanisms, relatively few of which are yet fully understood. One must therefore proceed by way of the steps outlined above. To save the doctor considerable trouble, electronic machines have recently been brought into use, for it has been found that they provide a sufficiently accurate degree of probability.

When the hypotheses have been arranged in the order of probability, it is necessary to verify them. The doctor must choose the most appropriate method of doing this and the one involving the least strain. In medicine, as in biology, the most satisfactory tests are those which give clear-cut results with the least complicated apparatus. Sometimes they will show a *lesion* situated in a definite place, or a particular *functional trouble* which will confirm the hypothesis; sometimes they will indicate a *pathogenic agent*. Recent technical advances fortunately allow such investigations to be carried out with a minimum of pain and risk.

## *Interpretation of lesions and functions*

Thirty years ago we should never have dared to imagine that it would be possible to reach a lesion in almost every part of the living human body, and to determine its form and microscopic structure. For a long time, we had to be content with seeing such things from the outside by X-rays. Only the air-filled lungs were visible, and X-rays showed them by natural contrast; other organs showed hardly more than their outlines, in so far as they differed in density from neighbouring tissues.

Very soon, it became possible to reveal ducts and closed cavities (pleura, peritoneum) by introducing a suitable contrast medium which was opaque to X-rays (barium, lipiodol, sodium iodide) or transparent to them (air). But in the early days of these researches, for which Sicard became famous, it was hardly believed that the most inaccessible and delicate vessels could be injected in the same way. Nevertheless, the cavities of the heart, the aorta, the pulmonary artery, the arteries of the heart and those of the brain, can now be made visible. More recently, the introduction of isotopes has made it possible to map out some lesions inside complete organs (such as the liver or the thyroid gland) and to discern the outline of a tumour.

For a long time, the need to record images on photographic plates, so as to see them with greater precision, restricted observation to a static view of organs and lesions. Only very recently has amplification of light made it possible to take cinematograph films of movements and, as the film unrolls, to discern slight changes that are not seen by static radiography, such as the appearance of cancers and peptic ulcers in their earliest stages.

But this is still only a question of relying on indirect observation; a direct view of lesions *in the living patient*, the supreme ambition of physicians and one hitherto available only to surgeons, has at last become possible, thanks to recent progress in endoscopic instruments. Optical apparatus can be passed into all closed cavities and hollow organs of a certain calibre (bronchi, oesophagus, stomach, ureter and bladder). Such apparatus makes it possible to see, to photograph, and to take ciné-films; and surgery is now so safe that it is possible to explore the lung, abdominal organs, or even the brain, without risk, when it is absolutely essential to *see*, without having to perform an exploratory operation for this purpose.

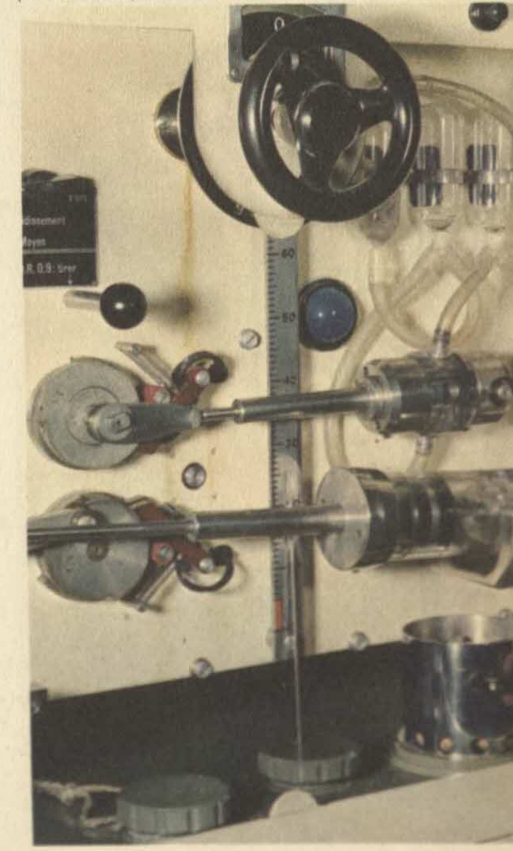
Direct vision, moreover, makes possible a form of investigation which is of very great importance: microscopic study. By the methods just described, it is possible to take samples of very small fragments of an organ from almost anywhere and to determine their nature.

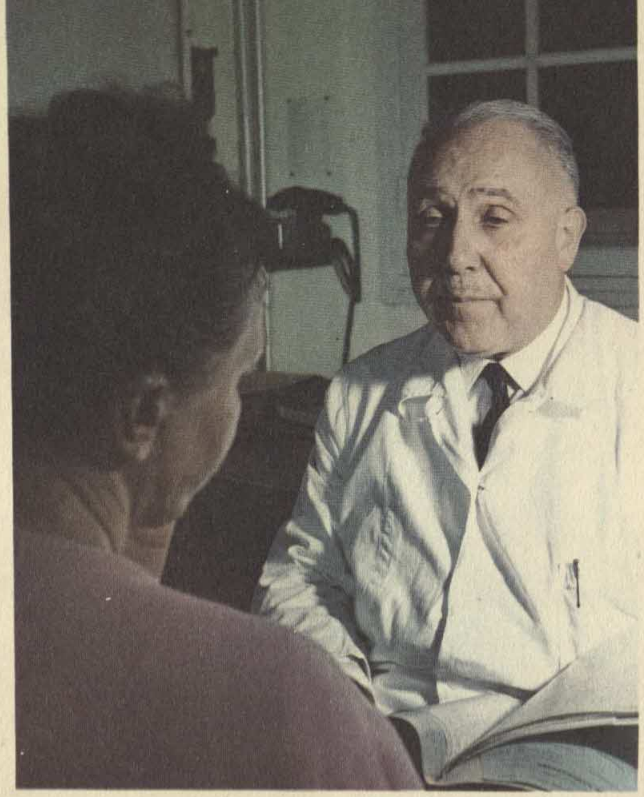
We have known for a long time how to count cells in the blood, in discharges, and in urine, and to interpret their significance. The method, recently introduced for general use by Papanicolaou, of making smears on slides, makes it possible to obtain fresh cells, not distorted by fixatives, and so to identify cancerous cells. Microscopic investigation nowadays involves more and more use of the electron microscope, which makes it possible to study disease at cellular level.

Not every disease reveals itself in lesions; but all of them disturb functions. Hence the need to explore the largest possible number of these functions. If some disturbance is revealed, the participation of one or several organs—which might never have been suspected—is shown, even in the absence of visible lesions.

A first approximation can be obtained by simple instruments: the thermometer, the graduated tube (to measure volume), the densimeter, the scales, and the manometer (for measuring blood pressure), which give information about the cardiac pulse (maximal pressure), about the peripheral resistance to circulation in the capillaries (minimal pressure)

*(Above) The Carpentier helium analyser for the measurement of lung volumes.*
*(Below) Detail of the metabograph: the feed pumps and instruments for measuring oxygen and potassium hydrate, the absorbant of carbon dioxide. (Photo Lod).*

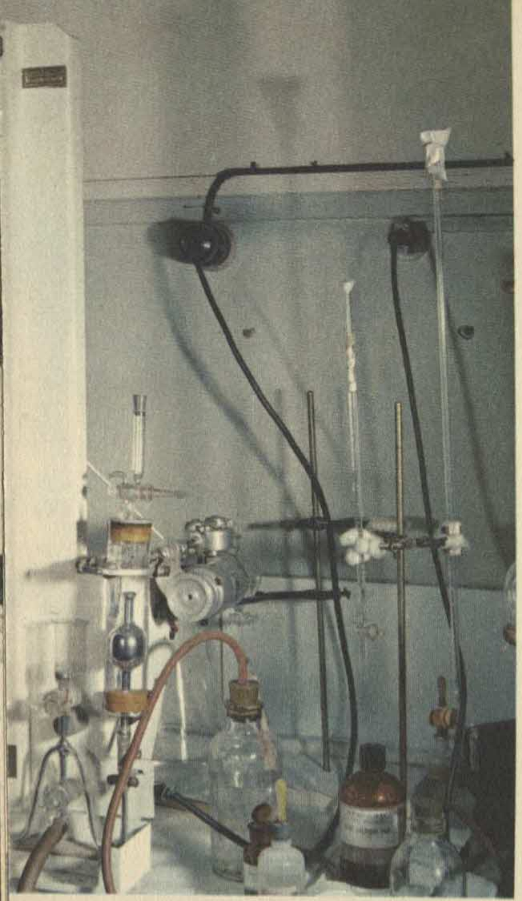




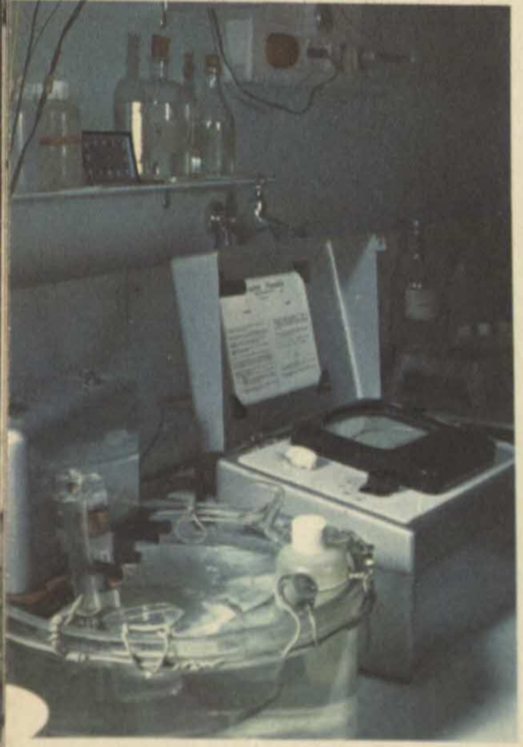
# The doctor and the patient

*The patient expects not only sympathy from his doctor, but feels a profound need for guidance and to be reconciled with himself. This is a far cry from the traditional attitude of approaching the disease without attempting to penetrate deeply into the patient's personality. The doctor should, on principle, neither dominate nor ignore the patient, nor should he seek to hide the truth. Identification of the disease, investigation of it, and finally its cure, are no longer the work of one man alone, who knows and dictates, but of two who seek knowledge and apply it. The patient nowadays is not a passive object, but a collaborator; the doctor is both instructor and guide. (Photo Lod).*

EN CAS D'INCENDIE



*(Above) Van Styke's pressure gauge apparatus for measuring blood flow.*
*(Below) Poncelle's haemocell and potentiometer for determining the pH of the blood at 37°C; the pH indicates the alkalinity of the blood. (Photo Lod).*



and about the elasticity of the arteries (amplitude of oscillations).

Progress in *physical* measurements has been such that one can measure the arterial and venous pressures almost everywhere and find the differences between them. By controlling the pressure-gradients of the pulmonary circulation, the general circulation, and the heart cavities, it is possible to reconstruct the hydraulics of the circulation. In 1958, Doctors Cournand, Richards and Forssman showed that a catheter passed into the peripheral veins of the arm could be carried to the right side of the heart without danger, which made it possible to take very precise measurements, which previously had been impossible.

Similarly, the volumes and pressures of the inspired and expired air of the lungs can also be measured; the pulsation of the arterioles can be registered, too, without doing any damage, due to electronic methods that we have developed with Dr Maurice Marchal.

Immense progress has also been made in the *chemical* investigation of the physiology of functions. For a long time, we had to depend on elementary analyses of urine (albumin, sugar, acetone bodies) and of the blood (urea, sugar, cholesterol). But today we can estimate chemically most of the metabolic and secretory functions. It is possible to tell, for example, how the kidney glomeruli filter the circulating plasma and how the tubules carry out their function of reabsorbing the filtrate in order to conserve elements essential for the maintenance of the internal environment; and how the liver eliminates pigments, fixes colloids, and stores up reserves of glucose or galactose.

The whole chemistry of respiration can now be studied quantitatively in all its aspects; oxygen and carbon dioxide, the proportion of oxygen fixed on the red cells and that of carbon dioxide combined with the blood constituents, and the alkalinity of the blood.

Thanks to our knowledge of physiology, we can recognize endocrine disturbances of the menstrual cycle, estimate the hormones eliminated in the urine, and tell how the thyroid gland fixes radioactive Iodine-131 and how it influences the combustion and consumption of oxygen (basal metabolism). One can measure the function of the suprarenal cortex and that of the genital glands by titration of urinary steroids (11-oxy-17 ketosteroids).

Although the pituitary, a very important gland, is enclosed at the base of the skull in the inaccessible sella turcica, there are methods by which its function can be detected: the function of the posterior pituitary is to secrete the oliguric hormone and decrease the secretion of water in the urine; the function of the anterior pituitary is to produce hormones which stimulate the secretions of almost all the other glands, thyroid, suprarenal, ovaries, and the corpus luteum.

Secretions, blood and fragments of organs are cultured in media chosen specifically, and viruses are inoculated into the allantoic membrane of the chick embryo. The conditions of culture, maintenance, and the transfer of these viruses into animals, must be very strictly determined. The nature of the tissues used must also be taken into account, because the organism contains growth-inhibiting substances.

Tissue culture, a technique introduced by Ross G. Harrison and extensively used by Alexis Carrel, has been applied to the detection of certain diseases. We know how to cultivate cancerous cells derived from human cancers, and to make direct analysis of human chromosomes in tissue culture.

Since 1958, cells of patients with congenital anomalies have been removed from the skin, the tendons, or the bone marrow and cultured. The number and form of the chromosomes are now known precisely, and also their anomalies. For example, R. Turpin, J. Lejeune and M. Gantier recently discovered a supernumerary chromosome in patients suffering from mongolism, a discovery quickly confirmed by C. E. Ford and P. Jacobs.

The enormous range of the methods and means of investigation makes it possible to detect almost all the details concerning the lesions and functions of a disease. But research must never be carried out blindly. It is necessary to reflect constantly in order to find the most appropriate method and to know what one expects of it. The cause and nature of a disease are discovered not by multiplying the number of investigations, but by strictly applying the basic scientific method of formulating and verifying a hypothesis. If this hypothesis is invalidated by the facts, it is necessary to begin reasoning again and to find new, conclusive results.

## *Knowledge of the sick person*

Detection of a disease is only one stage in its investigation, and with this alone the doctor cannot be satisfied. He must start from it to widen the field of his investigation and to gauge the reactions of the human being he is investigating to the general repercussions of the disease from which the patient is suffering.

The existence of a lesion or the peculiar disturbance of a function carries with it other disturbances which may concern organs often far apart, because the functions reciprocally control each other. No repercussions of this kind are more remarkable than those seen, for example, in diseases of the glands of internal secretion. It may be proved that the signs of a disease are due to an affection of the thyroid gland, but our knowledge of the disease would still be incomplete. Diminution of the secretion of this gland (thyroxin) lowers its level in the blood. When this level, measured by the amount of iodine bound to precipitable proteins, falls below 4–8 micrograms per 100 cc of plasma, the anterior pituitary is stimulated. This puts into circulation an increased amount of the substance (thyrostimulin) which induces thyroid secretion. Under its influence, the thyroid gland, paradoxically, increases its volume. It becomes goitrous, while its function is diminished. To understand the link between such mechanisms, it is necessary to know the whole system of their interconnections.

No estimate of the course of a disease or of its outcome (prognosis), and no treatments are valid unless they are supported by profound knowledge of the regulatory mechanisms of the body. In every case it is necessary to know in what measure the losses of function are compensated for by hyperactivity of other organs, how correlated functions operate to cancel out the deficit, and whether the regulation of the internal environment continues to be maintained.

This knowledge is acquired by the physiological and biochemical procedures already described. They are no longer used merely to track down isolated and significant signs of disease, but to reconstruct the whole picture of the disorder.

This reconstruction will not be complete if one loses sight of the fundamental problem: that of the psychological and nervous reactions. Many doctors do not give these reactions the attention that they deserve; moreover, the subject is imperfectly taught and the scientific study of psychological correlations is only in its infancy.

One patient suffering from a disease may be deeply depressed, yet he hides his depression behind a cheerful façade; others feel anxious, but without letting this be seen; their emotional exhaustion is more profound than is justified by their illness and their disease develops precisely because for a long time, and without admitting it, they have been at the end of their tether. Others again may have given up all hope and let themselves succumb; they repudiate not only the disease, but life itself. These states of mind, carefully dissimulated, may have organic consequences of great importance. They give the disturbances an amplitude, a diffusion, and an importance greater than those caused by the disease itself, by aggravating the symptoms and affecting the lesions.

The need for thorough investigation of the troubles that the illness provokes in the affectivity and sensibility and, in a more general way, in the personality of the patient, is just as imperative as the obligation to discover the organic disorders.

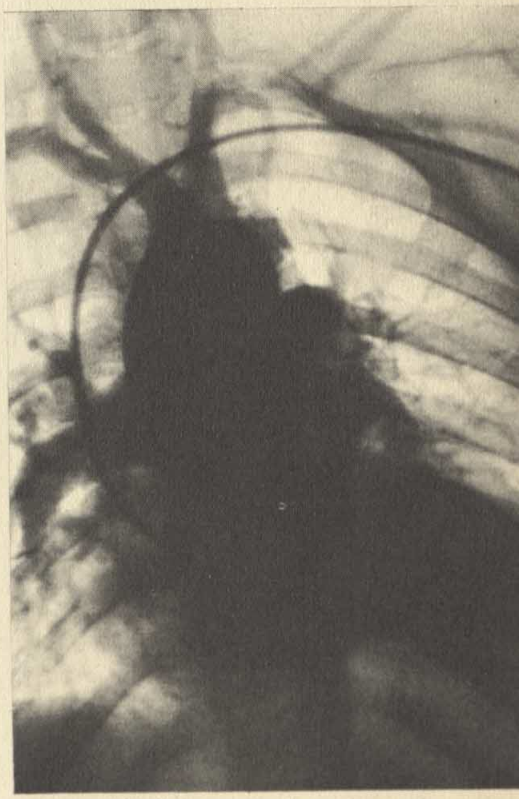
## *Treatment*

It is only after this long series of investigations that correction of these disorders can be successfully undertaken. Meanwhile, it is necessary to alleviate the symptoms and lessen the suffering. But this is not 'therapeutics'. In the modern concept of medicine, treatment does not consist of applying prescriptions or of administering remedies, but of carefully readjusting the displaced cogs of the living machine.

There are several ways of doing this: by chemical action, by physiological compensation, or by the deliberate suppression of a useless cog in the machine.

Physicians are now possessed of marvellous resources and consequently have abandoned the old adage: 'Let nature take its course.' The time has gone when the processes had to be left to themselves, sometimes for the better, but too often for the worse. They can now be directed. Nevertheless, the adage is still true. Medication must be applied with meticulous attention to dosage and with all the necessary precautions, by integrating it into the normal processes of regulation, so that these may reassert themselves, restoring equilibrium.

If this effect is not achieved, it may be necessary to curb a natural tendency to increase the dosage. Just as the disappointed experimenter must begin his investigations again, starting from other premises, so the physician must reconsider his problem, bearing in mind the possible intervention of an important factor that he has not perceived. But the comparision between the two is not fair; the experimenter has unlimited time before him, but the doctor is working against time. The clock of the disease ticks inexorably on. If compensation is too late, it will no longer be possible to re-establish normal re-



*Nowadays one can pass various forms of apparatus into all closed cavities, making it possible to see or take photographs. The radiograph above shows the introduction of a catheter into the right side of the heart through the vena cava. (Illustration by courtesy of Professor Kourilsky).*

*Radiograph of the breast. The star-shaped opacity in the middle of the picture corresponds to a deep malignant tumour. (Radiograph supplied by Professor Jean Gosset).*

adjustment because the intensity and duration of the functional disturbances will have created irreversible lesions or vicious circles. Thus the use of therapeutic substances (chemical substances, antibiotics, hormones, or corticoids) must never be decided upon without an extremely careful appreciation of what their effects will be on the body's regulatory mechanisms.

Generally speaking, the effect of most chemical substances when they penetrate into the organism is to initiate the formation of other substances antagonistic to them (antibodies): they are said to be antigenic. This property proceeds either from their molecular constitution (proteins or polysaccharides), or from the fact that they have become fixed on to certain compounds belonging to the organism itself (for example, proteins). The combination between the antigen and the antibody provokes inflamation or necrosis of the tissues. These reactions are characteristic of immediate or delayed hypersensitivity and can be very violent.

Thus it is obvious that the organism may be subjected to considerable risks by the unconsidered introduction of the most diverse substances. It can no longer be left to time to find evidence of lack of toleration, nor should prescriptions be repeated because no undesirable side-effects have appeared.

In medicine, as in chemistry, it is necessary to be on one's guard against chain reactions. Those who lack experience seldom suspect them, but when they do arise, the patient's situation can be endangered for a long time, if not permanently. Automatic, hasty, repeated, cumulative, or simultaneous use of diverse drugs is unscientific. It is true that the organism's ability to compensate is so great that even violent therapeutic agents are sometimes overcome and their effects corrected without the knowledge of the doctor, but that is no excuse for lack of decision or empiricism. Correction of the body's adjustments is safely accomplished only by establishing a well-laid plan of action and continuing with it for a definite period. Such a plan will only be successful if the doctor has a profound physiological knowledge of the regulatory mechanisms of the body.

It is a general law of physiology that exercise maintains function. It is conceivable, therefore, that restoration of regular function to a physiological entity may start chain-reactions, revive one or several deficient functions, and possibly achieve remarkable results. In fact, re-education of muscular, cardiac, respiratory, and digestive functions by exclusively physiological means and without any external stimulation is one of the most powerful means of ensuring a return to normal equilibrium. It is necessary to use such means systematically, even while the cause of the disease is still active, because more often than might be supposed, reconditioning of the functions makes it possible for the organism to eliminate the cause.

But one must not restrict oneself to making use of organic functions only. It is also necessary that the psychosomatic effects, the origins of which are emotional, should help to re-establish the co-ordination of the whole.

Experience has shown that whatever the disease may be, the reconditioning of the nervous system is a factor of outstanding importance. It is to this that we owe those sudden transformations which surprise and encourage many doctors. We know now that they occur when, consciously or unconsciously, a normal psychological state has been re-established and the patient is willing to make the effort to face his future again.

But more than this is required. The idea of regulation must be extended to the patient's environment. Often the 'deconditioning' which has caused the disease results from the prolonged action of several unfavourable factors: fatigue, or extreme psychological tensions in his personal or professional life. Once the cure has been achieved, it is necessary to ensure a suitable environment in order to prevent the patient relapsing or having a fresh attack.

The welfare of the patient is therefore far from being dependent on drugs alone. It will be much more certainly secured by a judicious combination of chemical, pharmacological, physiological and psychological results. None of these should be omitted in attempting to correct the mechanisms of re-adjustment.

Surgery, too, cannot be isolated from the context. Its objective, its timing, its immediate and remote consequences must be integrated into the physiological process of re-adjustment. Whether one operates to abolish a lesion, the presence of which maintains disease, or to re-establish certain regulatory processes by constructing new circuits (as in surgery of the alimentary canal or the vascular system), or even to remove a disturbing or dangerous effect by severing a conducting pathway, the decision to do so can be taken only as part of a general plan of action.

But if surgery, which emancipates the patient, has lost its independent role, it has gained in efficacy. Surgery today records a degree of success that no one would have dared to hope for thirty years ago, and this is because methods of conditioning the patient before, during, and after the operation have made extraordinary progress, and because the disturbances that occur during and after the operation are nowadays quickly corrected. These advances have made it possible to adapt methods which have been perfected to the highest degree by experimental surgery and the most advanced physiology.

## *Medical engineering*

Modern medicine is comparable with the work of the engineer, who patiently tunes up the machine. This comparison is particularly evident in the dramatic circumstances of the treatment of emergencies. Here, the reconditioning of the patient must be carried out without delay, sometimes as a matter of life or death. Miracles are wrought by scrupulously careful correction of disorders, re-adjustment of the internal environment, and precise replacement of lost substances (red blood cells, proteins, water, electrolytes, vitamins) in the necessary proportions. These various forms of treatment can be continued day and night, while the patient is either unconscious or kept in a state of hibernation, until the organ, which may have been subject to a major lesion, has re-established its function.

Every hospital now operates a resuscitation service. Persons who are comatose, poisoned, shocked, burned, or rescued from drowning, or those with heart disturbances or suffering from syncope or asphyxia, in short, victims of every kind of disaster, are nowadays resuscitated in numbers that could not have been hoped for ten years ago.

The work of the anaesthetist also belongs to the engineering aspect of medicine; he 'conditions' the nervous system to sleep by means of chemical substances and continuously corrects their effects throughout the operation, by constant control of the reflexes, respiration, blood pressure, pulse, chemistry of the blood, and renal excretion.

The more deeply medicine is studied, the more one is struck by its formidable complexity, and it is not surprising that attempts should have been made to simplify the subject, either by studying a number of diseases in the same organ (specialization), or by detecting anomalies before any symptom appears, as in systematic diagnosis.

The advantage of the first method is that the same investigations can be concentrated on the same group of diseases; its disadvantage is its propensity to ignore injuries to neighbouring or distant tissues, and this works directly against the understanding of the regulatory processes of the body.

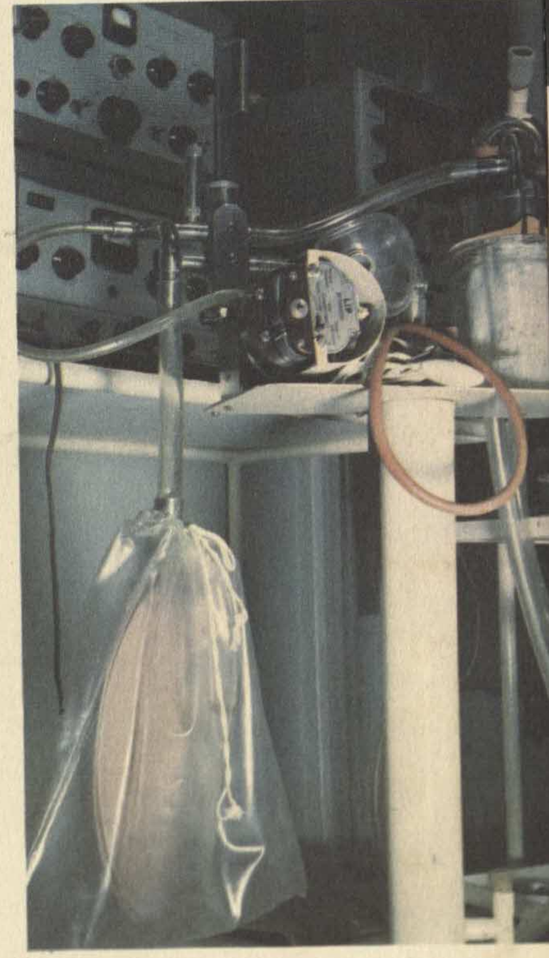
Investigation may be limited to one organ (eg, the lung) or to one disease (eg, tuberculosis). But one can also try to grasp the possible disturbance of a regulatory mechanism by making many systematic investigations or soundings.

This is the American check-up system. Its advantage is that the same examinations can be made on a large number of individuals in a short time. It is justified when it is necessary to protect mankind against a transmissible disease which threatens it (tuberculosis), or against a disease which rapidly becomes incurable (cancer), or against progressively dangerous metabolic disturbances. Its results are undeniable, but once the disease has been detected, it will be necessary to examine in detail both the organism and the patient by the complex method already described.

It is understandable that there has been a desire to simplify this method, for example, by going directly to the biological disturbances without concerning oneself with the symptoms. For a long time the hope was cherished that the systematic multiplication of tests would make it possible to identify diseases almost automatically. But this illusion no longer exists. Understanding of human disease comes through man. Nothing has yet replaced the procedures that have been briefly dealt with here. Nothing alters the fact that man is an entity and should be studied and reconditioned individually.

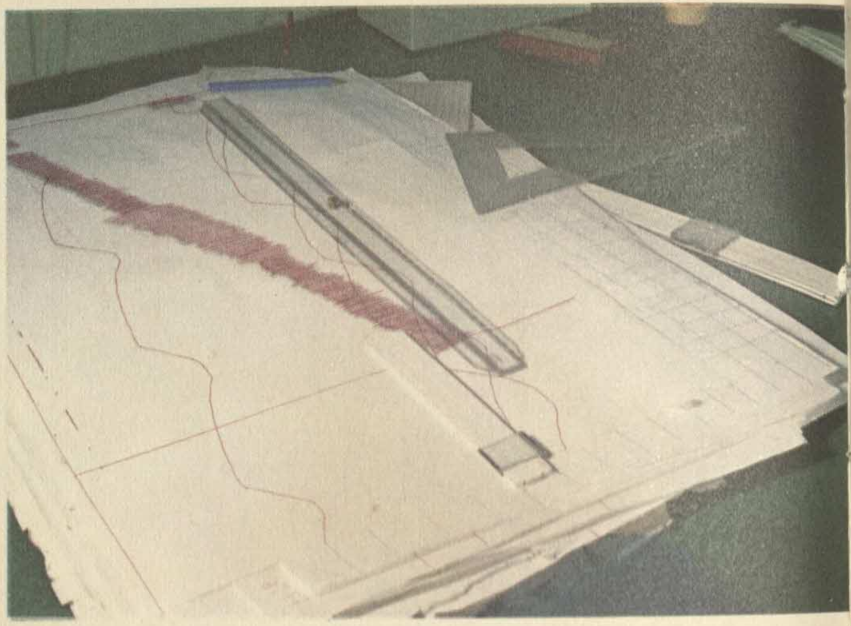
Nevertheless, the more scientific medicine becomes, the more investigation is prolonged, and the more restricted is the number of patients that the doctor can examine and treat properly. Though there is mass prevention of disease, we cannot have mass medicine, because the guarantee of success diminishes in proportion as the number of patients increases and as time is lacking. But, paradoxically, the doctor's success tends to be judged by the number of patients he examines and treats.

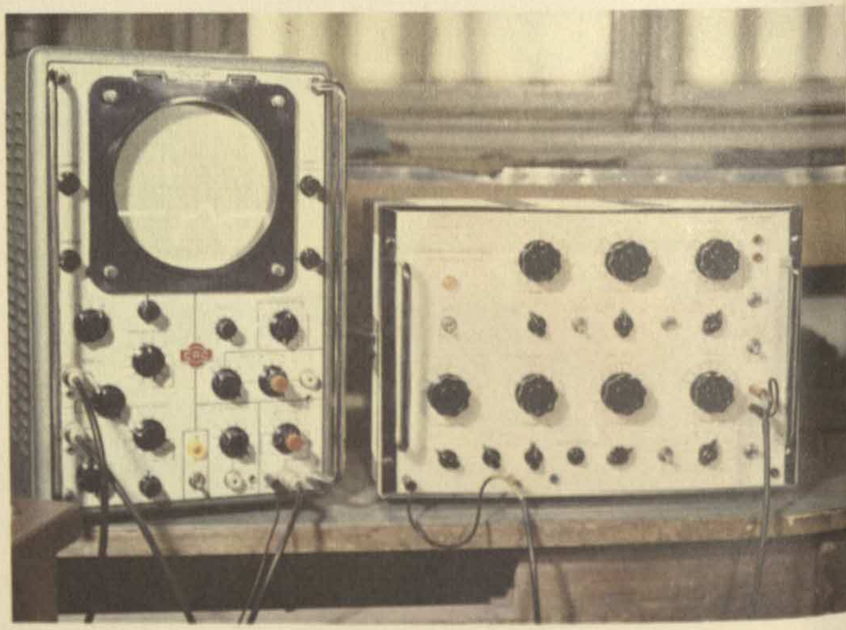
For medicine to remain efficient and humane, the 'Science of Man as a patient' must provide the highest degree of efficiency for everyone. The organization of medicine therefore needs to be thought over again. The sympathy which a man has for others of his kind in difficulty will finally be measured by his attitude towards the suffering, the life and the death of the most humble among them.



*Artificial respirator. (Photo Lod).*

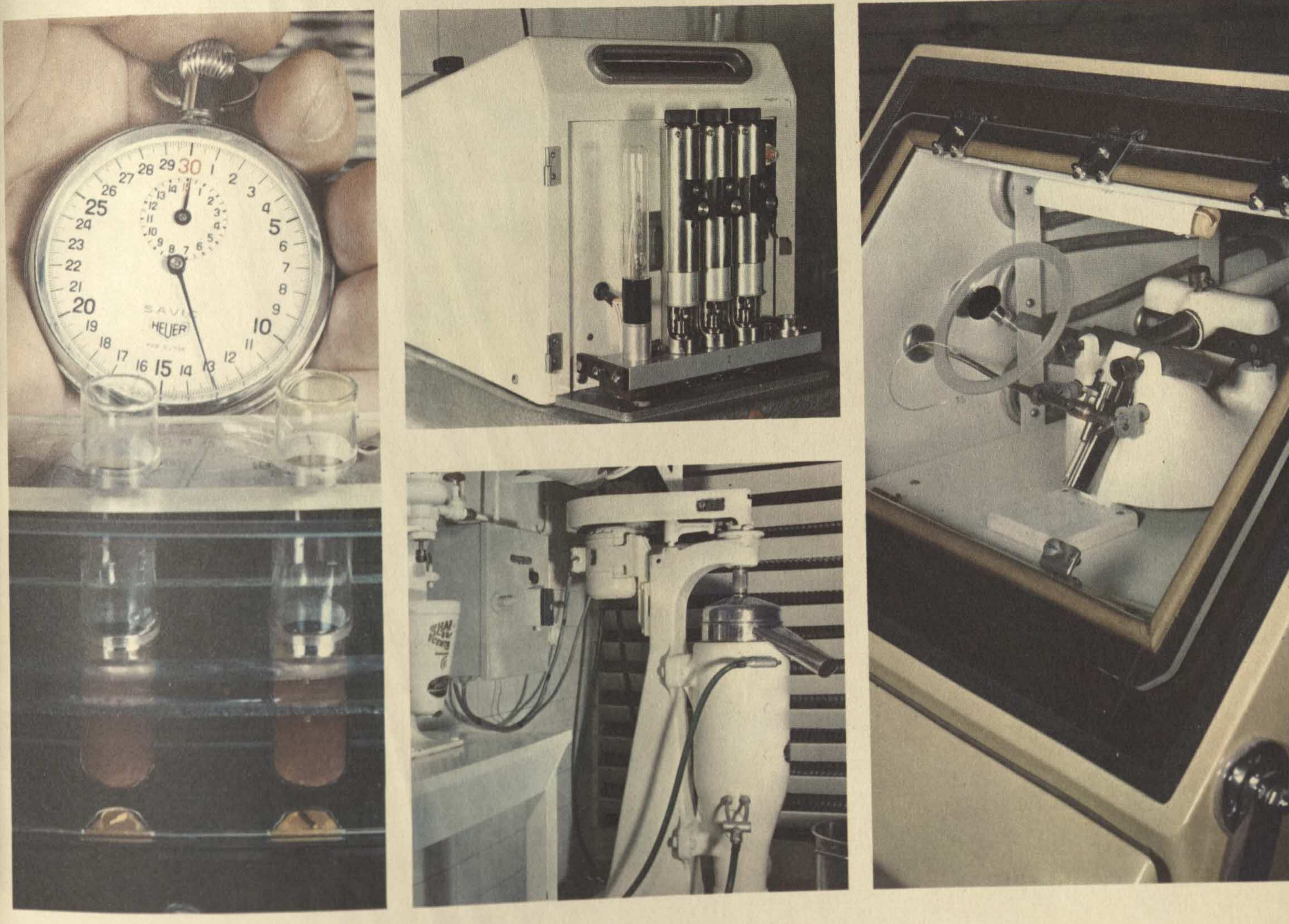
# PART ONE





*Medicine now has at its disposal a considerable wealth of methods and means for diagnosing a disease in almost all its details, lesions and functions. But investigations must never be performed blindly. It is always necessary to reflect, to find the most appropriate method, and to know what one expects from it. Light is thrown on the cause and nature of a disease not by multiplying the number of examinations,*

# *Detection and diagnosis of lesions*



*but by strictly applying the basic scientific method of formulating and verifying a hypothesis. Here we see some of the investigating procedures that contemporary medicine uses. From left to right and from above downwards: Examination of cells by the electron microscope; a spirograph; cathode-ray oscillograph; measurement of the coagulation time of the blood; centrifuge; and finally, a cryostat, an apparatus for cutting microscopic sections of fresh tissues at low temperatures down to —30°C. (Photos by Lod). Those on the left, taken at the Hôpital St Antoine, Paris; in the centre, at the 'Jean Julliard' Centre de Transfusion Sanguine de L'Armée; those on the right, at the Centre d'Etudes et de Recherches de Médecine aéronautique.*

# The localization of lesions

### *Maurice MARCHAL*

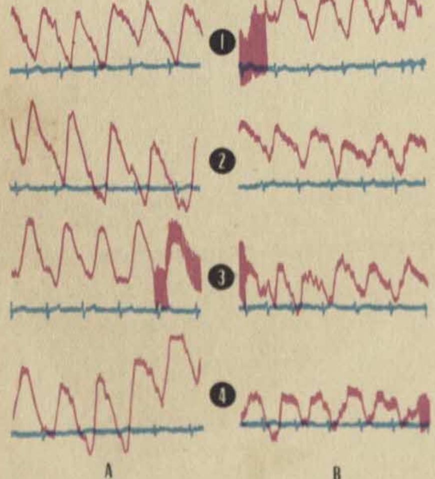


*Fig. 1. Record of the 'pulmonary pulse' on the cinedensigram. In A, for the left lung, the cinedensigram is normal: Note the large amplitude of the pulsation and the agreement with the electrocardiogram. In B, because of lesions of the right lung, the pulsation is clearly feebler and more irregular. The four tracings, one above the other, correspond to four different parts of the lung: 1. the upper region; 2. the hilar region; 3. the median area; 4. the basal region.*

The use of X-rays for the detection of lesions and functional troubles is only about half a century old. It was while Wilhelm Konrad von Röntgen was studying the working of a Crookes tube in his laboratory at the University of Würzburg that he noticed, on November 8, 1895, a new phenomenon: at the point of their impact on the glass of the tube, the cathode rays caused a bluish, fluorescent spot, which itself emitted rays capable of darkening photographic plates, even when these were enclosed in an envelope of black paper. He also noticed that paper covered with barium platino-cyanide shone under the influence of these unknown rays. Shortly after this, Röntgen made a radiograph of his hands; he established that the rays penetrate soft tissues, but are absorbed by dense tissues, such as the bones, which are thus made clearly visible by contrast.

## *Static radiography*

In 1896, this discovery was communicated to the Academy of Sciences in Paris. It was then that Béclère and Bouchard made the first radiographies of patients. In the same year, the first observations were published on a red and persistent cutaneous eruption which followed the exposure of the skin to X-rays. These eruptions were the first cases of X-ray dermatitis.

In radiography, certain conditions are necessary to obtain clear images without distortion. In the original apparatus the X-rays were propagated from the anticathode in the form of a cone; this enlarged the size of the object situated near the tube and deformed it.

Later, to avoid these deformations, *teleradiography* was invented. This made it possible to arrange for a distance of 2·50 m between the object and the tube and to use only the central part of the radiation cone: the rays are then approximately parallel and do not deform the object. Exact measurements of the object, for example, the heart, can then be made directly on the radiograph *(orthodiagraphy)*.

The visibility of the object is due not only to its own atomic density, but to the contrast between this and its surrounding tissue, composed of substances of lower atomic density. It is for this reason that the contours of muscles are not well-defined, because they are surrounded by tissues of the same density, while the lungs, filled with air, are clearly visible and the shadow of the heart projected on them is clearer still.

The precision of the image depends on the complete immobility of the object. If organs are moving, the exposure to radiation must be short enough to snap them without movement showing on the film. Thus, if one takes a radiograph of the heart during its contractions (systole), the exposure should be only 1/100th of a second and during relaxation of the heart (diastole) 1/20th of a second.

Exposure times of the same order are also necessary for radiography of the lung, which is irrigated by pulmonary arteries coming from the right side of the heart.

For the stomach and duodenum, a tenth of a second gives good radiographs; for slower movements, such as the contraction of the gall bladder and pelvis of the kidney, exposures of one-third or half of a second give good results.

To obtain really clear definition in a radiograph it is necessary to eliminate secondary radiation, which is the result of projection and of the object radiographed. This is achieved by means of filters made of fine strips of lead arranged parallel to the incidental radiation (the diaphragm of Potter-Bucky); it is also necessary to use X-ray tubes with very small focal spots (the smallest have an anticathode the sides of which measure 0·3 mm.

How does one eliminate errors due to the superimposition of images? In spite of all precautions, the interpretation of shadows visible on the film is never simple. Tissues and organs are, in fact, not homogeneous and the

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various planes in them superimpose themselves on each other; there is thus a summation of the shadows; artificial images can appear. Conversely, cancellation of shadows can result from the interposition of air in front of or behind the image (for example, in the lung or the abdominal cavity).

One method of avoiding such errors is to use sectional radiograms or *tomograms*. This technique makes it possible to analyze tissues section by section and to eliminate the summation of shadows. Its principle is to make the X-ray tube and the radiographic film move simultaneously and in opposite directions around a pivot in the centre of the patient's body during the exposure. Tomography makes it possible to isolate the lesion from shadows in front of or behind it and to reveal anomalies which are not visible in radiographs taken frontally; its use is necessary in the radiological exploration of the lung, of bone, of the vertebral column and of the larynx. It makes it possible to analyze the object completely, both frontally and in profile.

An improvement on this method is serial tomography. Several tomographs are made simultaneously, so that each one shows pictures of the various planes corresponding to their distance from one another. The duration of exposure to the X-rays is thus lessened.

To dissociate superimpositions of images one can take an enlarged radiograph. The image is enlarged two or three times, as is also the distance of the pathological structures in relation to each other, so that superimposition of images is avoided. But for this technique X-ray tubes are required which have very fine focal spots (0·3 mm squares) instead of the normal size of 1 to 2 mm, which cause a blur. One cannot, however, decrease the size of the focal spot indefinitely because the charge on the anticathode then becomes such that it is volatilized.

Electronic focusing of the tubes by means of electromagnetic lenses has recently made it possible to give the radiogenic focal spot which emits the X-rays a much firmer definition.

Another method of dissociating superimpositions is radiography in relief; this is known as *stereoradiography*. Two radiographs of the same region are taken by separating the two radiogenic focal spots by at least 7 cm; this distance corresponds to that of the average separation of the eyes. By this method one can examine the two negatives by special stereoscopic devices and obtain a very clear impression of relief.

## *Dynamic radiography*

By recording the visible movements of the internal organs on the radiographic screen, radiology can be used for physiological studies.

'Radiological physiology' gives much more complete information than simple static radiography by which only anatomical study is possible. It is continually improving its methods.

I. The oldest method is *radiokymography*, invented in Germany in 1911 by Goett and Rosenthal. This consists in causing a lead plate, pierced by horizontal windows, to pass between the subject and the film during the radiography. The heart and the great vessels inscribe their beats directly on to the film.

II. Cineradiography, following the work of Comandon and Dauvilliers, has only recently become a practical method. It consists in making cinematograph films on the radioscopic screen. It results from the perfection of the electronic telescope, used during the Second World War to reveal the movements of the enemy at night, which made it possible for Professor Lallemand, of the Paris Observatory, to construct brightness amplifiers, thanks to which the movements of deep organs, visible on the radioscopic screen, can be cinematographed. The photons of the X-rays, projected on a photocathode situated in the brightness amplifier, are directly transformed into electrons, the speed of which is considerably amplified by electrostatic or electromagnetic lenses. The increase of the luminosity becomes such that one can examine patients in full light.

III. *Radioscopic television* is now, thanks to the stimulus given to it by French research workers (Porcher, Noix, Cherigié, Djian), currently used; darkness is no longer necessary in the radioscopic room. The diagnosis of images of the digestive tract the interpretation of which is difficult (for example, ulcers, cancers of the stomach or colon) can be made directly on the television screen.

IV. Records of the movements made by photo-electric cells are also used. Records of moving radioscopic shadows can be made by methods even more sensitive such as those that we have invented since 1934 (M. Marchal, Hôpital Tenon, Paris) and have used clinically with R. Kourilsky since 1949. These methods make use of photo-electric cells and photo-multipliers sensitive to X-rays which make it possible to record the 'pulmonary pulse' in man; that is to say, the

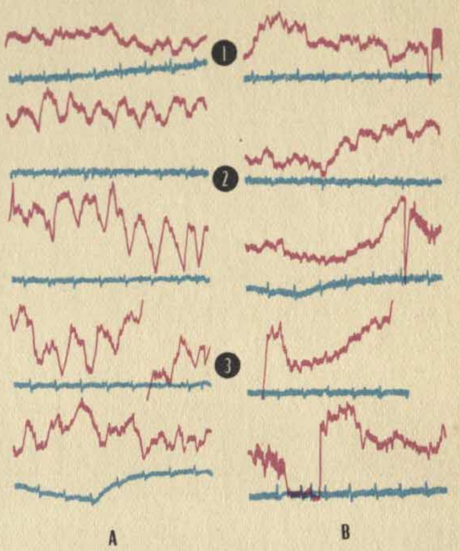

*Fig. 2. Cinedensigram of a patient with cancer of the left lung. The right lung (A) shows waves that are fairly normal throughout their height, except at the summit (1). The left lung (B) shows complete arrest of the pulsation. There is no correlation between the pulsations and the electrocardiogram simultaneously recorded: 1, apex of the lung; 2, middle region; 3, base of the lung.*

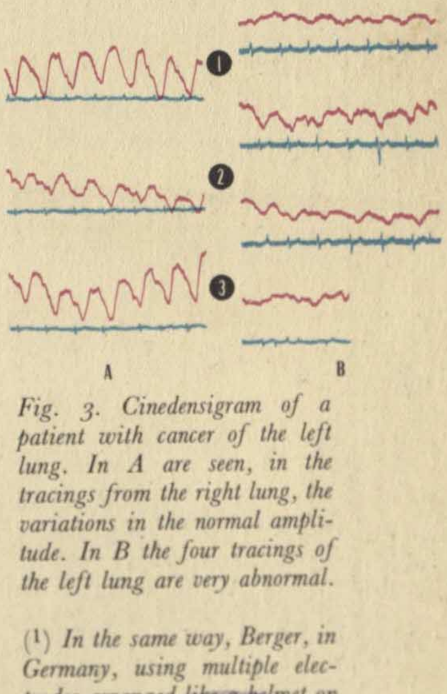

*Fig. 3. Cinedensigram of a patient with cancer of the left lung. In A are seen, in the tracings from the right lung, the variations in the normal amplitude. In B the four tracings of the left lung are very abnormal.*

(1) *In the same way, Berger, in Germany, using multiple electrodes arranged like a helmet on the skull, has perfected* electro-encephalography, *which has made it possible to detect epilepsy and cerebral tumours.*

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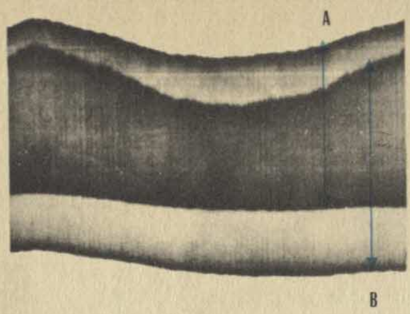

*Fig. 4. Simultaneous statidensigraphic record of the pulmonary ventilation in the two lungs. In A, tracing of the right lung; in B, tracing of the left lung. The two statidensigrams are not parallel; the left lung breathes much better than the right.*

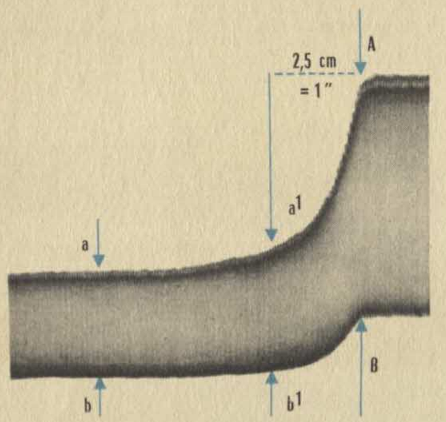

*Fig. 5. Test of forced expiration made on one lung of a normal subject; deep inspiration (AB), followed by an expiratory exponential curve ($a^1$, $b^1$, ab).*

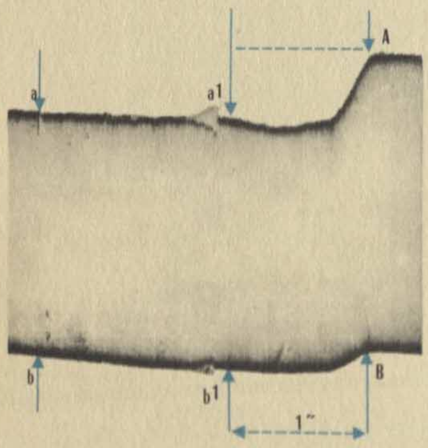

*Fig. 6. The same test made on a patient with emphysema. It will be seen that, after a brief expiration (the line $Aa^1$) the patient cannot expel the pulmonary air ($a^1$, $b^1$, ab).*

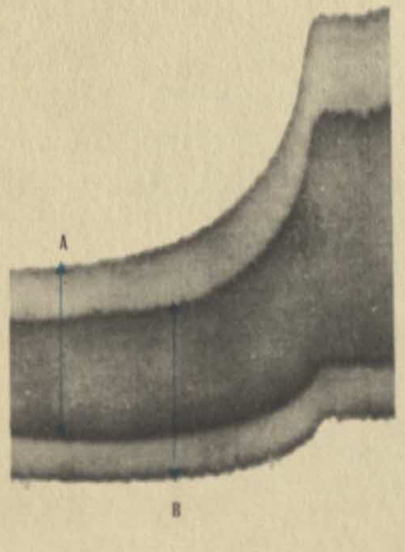

*Fig. 7. Separate and simultaneous statidensigraphic records of the two lungs in a normal person. A, right lung; B, left lung. In this case the parallelism is almost perfect.*

rhythmical distension and contraction of the calibre of the pulmonary arterioles at the periphery of the lung, which are normally invisible (*cinedensigram*; figs. 1, 2, 3).

The pulsation is studied in relation to the simultaneously recorded electrocardiogram, and an automatic calibration shows the relative quantity of X-rays which reach the cell in spite of an interposed opaque substance.

By this method it has been established that, in cancer of the bronchus, the pulsations are often abolished. This is the phenomenon of the arrest of the pulsation in the arterioles at a distance that is seen in cancer of the lung. Experience has shown that in a case of this kind it is difficult, in spite of appearances, to extirpate the cancer and that the prognosis is bad. It is possible, by applying the same recording method to the pulsating peripheries of mediastinal tumours which are in contact with the great vessels and the heart, to distinguish the tumours from the aneurysms before any surgical operation is carried out (M. Marchal). The pulsation, recorded in relation to the electrocardiogram, is, in fact, different from that of the vessels; conversely, the photoelectric cell, the sensitivity of which is very much greater than that of the eye, makes it possible to detect pulsations on a tumour which appears immobile to the most experienced observer but which is nevertheless an aneurysm.

If one uses this method to explore the border of the heart, one can detect anomalies in the pulsations (paradoxical systolic expansion), which reveal the persistence of an area affected by a myocardial infarct, although the electrocardiogram may have become normal. The importance of this discovery for prognosis and treatment will be realized.

Again, thanks to photoelectric cells, one can measure precisely the variations in the luminosity of the pulmonary image during respiration (the *statidensigraphy* of M. Marchal) and obtain curves that can be exactly superimposed on those which show the volumetric variations of the lung. One can register spontaneous respirations of the left or right lung, either separately or simultaneously without the knowledge of the patient; one can calculate the part played proportionately by each lung in the total ventilations, detect the absence of respiration in a lung that is clear and apparently normal, and establish the existence of a lack of respiration characteristic of emphysema (figs. 4, 5, 6, 7 and 9). In the same way one can explore partial diminution of respiration in different areas of the lung and proceed to a detailed local analysis of ventilation.

By combining the exploration of the circulation with that of ventilation, it is possible to estimate the respiratory function by means of coefficients that are very close to those furnished by direct investigations, but are obtained in a very short time and are characteristic, not only of the ventilation, but also of the pulmonary circulation.

## *The use of radioactive substances*

Since the discovery of radio-isotopes, which are radioactive substances produced artificially, either in an atomic pile or in a cyclotron, these substances have been used to follow variations in the circulation. When they are introduced into the general circulation, one can, in fact, investigate the local radioactivity of the organ that receives them and thus obtain physiological information of the greatest importance.

For example, the diffusion capacity of the alveolar membrane of the lung is estimated by radioactive oxygen administered by inhalation. The record is made by Geiger and scintillation counters (thoracography with radioactive oxygen). This must be done very near to the cyclotron because the half-life of radioactive oxygen is very short.

The speed of the arterial circulation is measured by means of radiosodium injected into a vein of the arm, detection being carried out in a blood vessel in the foot (in a normal person the time interval is 45–55 seconds); it is increased to 80 seconds in patients suffering from arteriosclerosis).

The same method is used to determine

whether there is a communication between the right and left sides of the heart (*isotopic radiocardiography*).

Cerebral tumours are detected by isotopes that emit beta rays, especially radioactive phosphorus. When the scintillator is brought near the tumour, the rate of the count exceeds the normal by almost 100 times.

Since 1945, detection of thyroid anomalies has been carried out by means of radio-iodine 131 (the half-life of which is eight days), because the thyroid gland specifically absorbs iodine. Every non-functional zone is shown up by a gap in the autoradiographic picture. One can thus establish a functional map of the organ and discover the secondary tumours of thyroid cancer disseminated in other organs. In the same way, the existence of tumours inside the liver that are not made visible by X-rays (cancers, a growth, a cyst or an abscess) is revealed by radioactive rose bengal (Caroli).

Isotopes are used in many other diseases. All the tissues have been explored and all forms of metabolism have been studied. The method is being widely expanded because its possibilities are vast, but it is not free from danger because of the possible consequences of radioactivity.

## *Other recording techniques*

One can gather important information about the local circulation in the tissues by recording variations in their electrical resistance (impedance) by means of high frequency currents. This has been applied to the arteries of the limbs, to the thoracic circulation (Atzler, 1932), and to the cerebral arteries, but it is not possible by this method to define the exact point on the pulsating organ that is being recorded and consequently to localize the lesions.

On the other hand, ultrasonics (used at frequencies of about 800,000 cycles per second) can be used for this purpose. As they leave the tissues they are received by suitable receptors which make it possible to record their absorption and to reconstruct a kind of 'ultrasonic image' of the tissues traversed. In this way one can detect cancerous tumours in the brain and breast, because absorption of cancerous tissue by the ultrasonic waves is clearly greater than that of normal tissues. The interventricular septum of the heart, which cannot be demonstrated by radiography, becomes visible by this method, which is used by the German School.

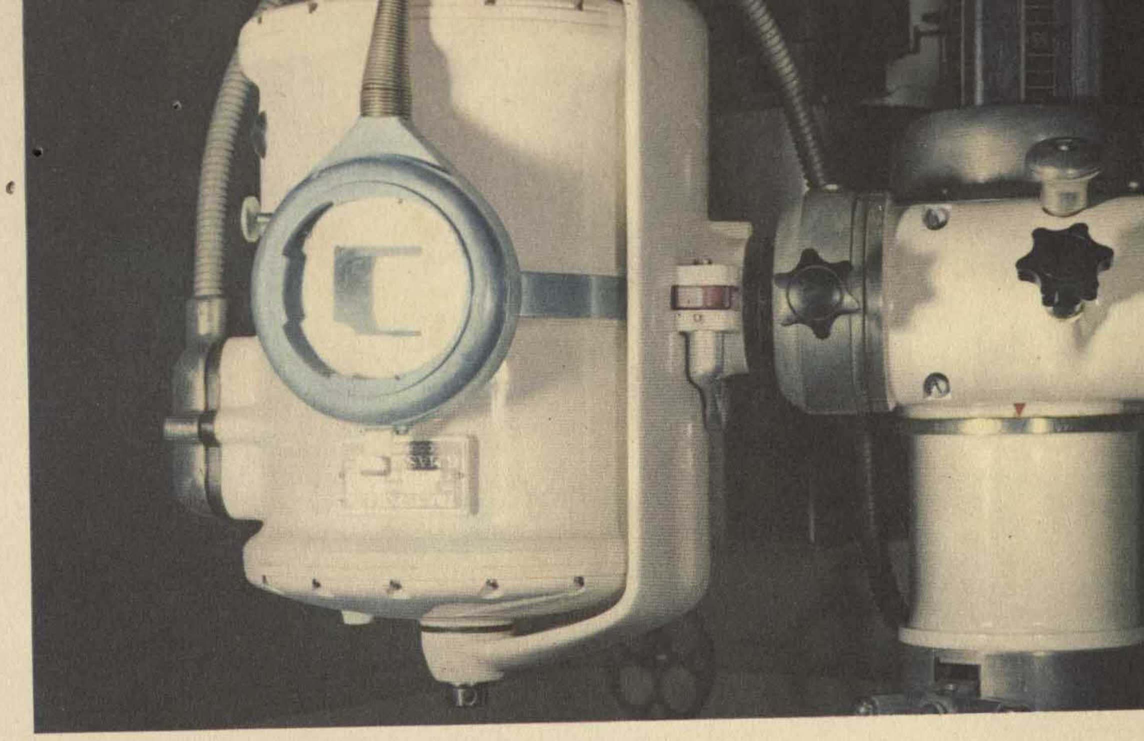

*Fig. 9. Röntgen tube in its protective casing. (Photo Lod).*

Finally, let us mention the recording of the recoil wave provoked by contraction of the heart on the human body by various methods, notably electromagnetic (ballistocardiography). The vibrations are transmitted to a metallic rod placed on the legs of the patient, who is extended on an elastic or suspended bed. The chief use of this method is for the detection of atherosclerosis and infarcts of the myocardium.

It is equally possible to localize lesions by recording the bioelectric currents. It is known that when a muscle contracts, it gives rise to an electric current. It was thus that Einthoven recorded variations in the currents produced by the heart, and perfected *electrocardiography* (discovered by various European experts since 1840), which makes it possible to detect an infarct (an area of modification caused by occlusion of a branch of the coronary artery of the heart) and to localize the lesion with great precision.[1]

*Electromyography* makes it possible to record disturbances of muscular contraction, as well as affections of the motor neurones and to do this in different groups of muscles: skeletal muscles (by means of the needle electrode invented by Adrian and Bronk in 1929), electro-oculography, electroretinography.

To sum up, it will be seen that, by adopting and perfecting the methods of radiophysics and of electrical recording, the detection of internal lesions which, even a short time ago, was unthinkable, has made considerable progress in the space of half a century.

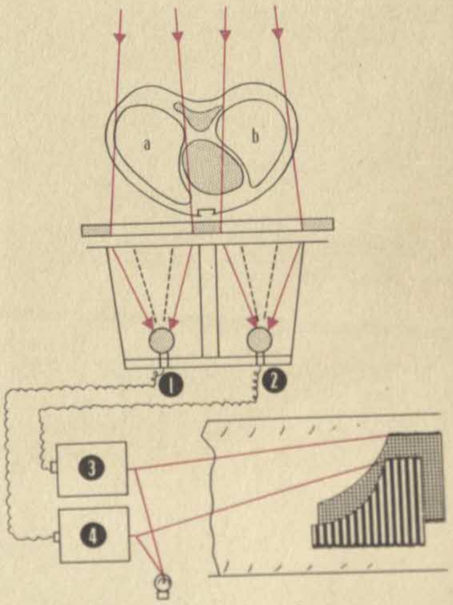

*Fig. 8. This diagram shows how a statidensigraphic apparatus works. From above downwards, a section of the thorax of the patient;* (a) *right lung;* (b) *left lung), then the screen with the box containing the two photomultipliers (1 and 2), separated by a partition. Below, the two tracings recorded simultaneously with the aid of the two amplifiers (3 and 4).*

# The investigation of functions

*Jean-Louis BONNET*

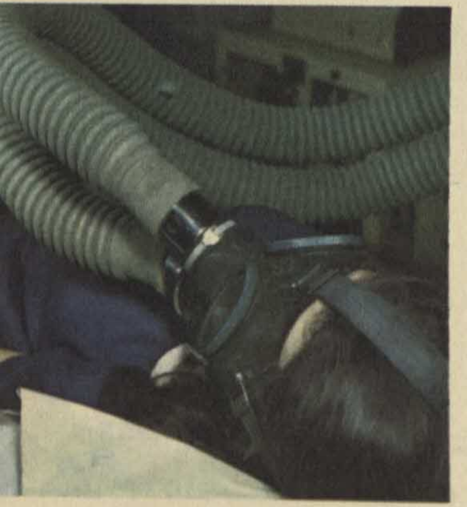

*Fig. 1. Spirographic examination. The closed-circuit respiratory apparatus is applied to a patient's face in order to record a spirogram. Note the two tubes, for the supply of oxygen and the exit of the respired air. (Photo Lod).*

To explore the function of the lung, one must study gaseous exchange and blood circulation in the lung.

The function of the lung is to transform venous blood, rich in $CO_2$ and poor in $O_2$, into arterial blood rich in $O_2$ and poor in $CO_2$. This alteration in the blood is effected in the pulmonary alveoli by contact between blood and inspired air through an extremely delicate alveolar-capillary membrane which allows the diffusion of the gases.

## Gaseous circulation or ventilation

Ventilation is studied by spirography. The patient breathes into an air container and variations in its volume are marked on a recording cylinder. In the container is soda-lime which absorbs the $CO_2$ eliminated by the lungs. The following successive records are made:

1. *A tracing taken with the patient at rest;* a spiked graph which tends upwards and indicates *(a)* the volume of air used in each respiratory movement, or the tidal air; *(b)* the respiratory rhythm; *(c)* the consumption of oxygen which expresses the general gradient of the curve, which itself expresses the diminution of the volume of the container, due to the removal of oxygen because the carbon dioxide is absorbed (fig. 3).

2. The *vital capacity* (VC), measured by making the patient perform a forced inspiration followed by a forced expiration. It includes the reserve inspiratory volume, the tidal volume, and the reserve expiratory volume (fig. 3).

3. *The maximal expiratory volume per second* (MEVS) is determined by making the patient perform, after a maximum inspiration, a forced expiration as rapid and complete as possible. The record is made with the recording cylinder rotating more rapidly than for the preceding investigations.

The terminal flattening of the curve shows the progressive diminution of the output, which expresses the increase in the resistance due to the decrease in the calibre of the bronchi during expiration. Normally, the lungs expel three-quarters of the vital capacity in one second (MEVS/VC=0·75 (fig. 4)).

In diseases which reduce the calibre of the bronchi, the curve is spread out and MEVS/VC is less than 0·75.

4. *Broncho-spirometry* of each lung records simultaneously the ventilation of each lung by introducing as far as the bifurcation of the trachea a special sound with two channels in it. By this method one can find out not only the ventilation of each lung, but also the consumption of oxygen by each of them.

Additional information about ventilation can be obtained by:

1. *Radioscopy*, which shows the movements of the thoracic wall and the darkening of the shadow of the lung during expiration when it empties itself of air. If a very limited area of the lung is not ventilated, its illumination will remain unchanged.

2. *Statidensigraphy*, by which it is possible to record the variations in the optical density of a lung exposed to X-rays, measured by a photo-electric cell.

## Chemical composition of alveolar air

The alveolar air, which is in almost direct contact with the blood, has a composition approximately the same as that of the air expelled at the end of expiration. This air is therefore collected and a chemical analysis can be made of it, though this is a very difficult process.

## Study of the blood circulation

There are two quite distinct aspects of this:

1. *Quantitative:* the measurement of the amount of blood flowing through the lungs, or the cardiac output, which is studied together with the physiology of the heart.

2. *Qualitative:* the study of the gaseous composition of arterial blood. It expresses the result of the gaseous exchanges in the lungs.

Blood is withdrawn from any of the peripheral arteries. One determines successively its $CO_2$ content, expressed in volumes per cent, and its oxygen content expressed either in volumes per cent or in the percentage saturation of haemoglobin. Normal values are 45 volumes per cent of $CO_2$; 20 volumes per cent of $O_2$; haemoglobin saturation 98 per cent. These examinations can be made with the patient at rest or after exercise, so that the flexibility of adaptation can be indicated.

In respiratory insufficiency, the arterial blood is poor in $O_2$ and rich in $CO_2$; this is known as hypercapnia.

## *Investigation of heart function*

We have seen that the functional investigation of the lung cannot be separated from that of the cardiovascular apparatus, because the heart, after it has pumped blood into the pulmonary vessels, sends it on into the general circulation. Its function is, in fact, to provide the tissues with the supply of blood that is indispensable to them.

The heart is thus made up of two synchronized pumps, a right and a left, separated by two vascular systems: the pulmonary circulation, the blood in which acquires $O_2$ and loses $CO_2$; and the general circulation, the blood in which supplies the organs with the $O_2$ that they need and takes up $CO_2$, the waste product of combustion.

Investigation of the functions of the heart therefore includes: calculation of cardiac output (that of the right and left hearts being, of course, the same); measurement of the distribution of pressures in the different parts of the circuit and in the cavities of the heart; determination of the volume of the heart cavities and of the possible deviations from the normal in the vessels, depending on circumstances; the study of the functioning of the heart muscle by recording its electrical activity.

## *The cardiac output*

This is measured according to Fick's principle. All the oxygen absorbed during pulmonary respiration (oxygen consumption or C) is fixed by the blood. If, while the blood is passing through the lung, 1 cc of blood fixes X cc of $O_2$, C cc will have been fixed by C/X cc of the blood that will have passed through the lung.

It is easy to measure the oxygen consumption of the lung, which is 250 cc per minute. The oxygen content of arterial blood is 0·20 cc per cc of blood. The oxygen content of venous blood is 0·15 cc per cc of blood, which must be taken in the heart itself by catheterization of the heart before the blood has been drawn off.

The output per minute is therefore $250/(0{\cdot}20-0{\cdot}15)=5{,}000$ cc or 5 litres, for a normal adult.

The pressures are measured in a vein of the arm by introducing into it a needle connected to a water manometer. The normal pressure is 10 cm of water. In an artery, the value of the arterial pressure is normally 130 mm of mercury.

In the heart cavities measurements are made by catheterization, that is to say, by passing a long catheter through a vein of the arm until it reaches the cavity of the right side of the heart: in the auricle, the pressure is −2 mm of mercury at relaxation (diastole), and +2 mm of mercury at contraction (systole) of the heart.

It is more difficult to measure the pressures in the left side of the heart. This can be done, however, by introducing a needle into the left auricle, either through the thoracic wall or through the left bronchus.

## *Volume of the cavities of the heart and of the blood vessels*

This is studied by radioscopy and by angiocardiography. Moving the patient under

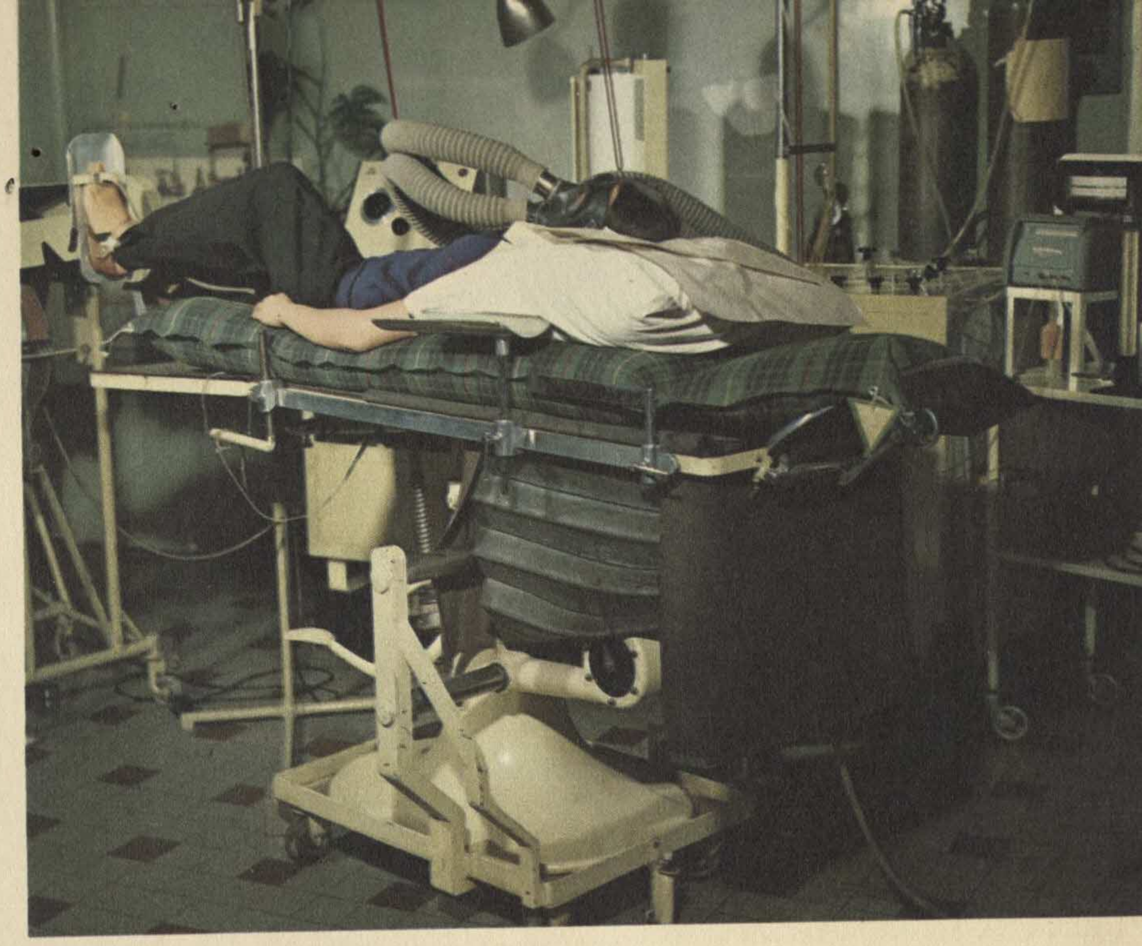

*Fig. 2. Recording of a spirogram: right, the recording apparatus; in the background, bottles of oxygen. (Photo Lod).*

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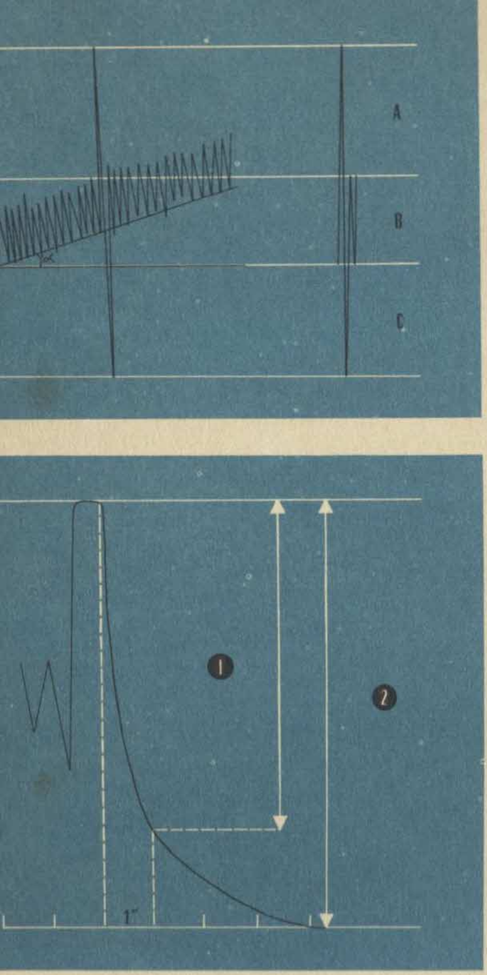
(1) C: *clearance;* P: *concentration in the plasma;* U: *concentration in the urine;* V: *volume of urine filtered in one minute.*

(2) Urography: *the radio-opaque substances that are used are iodine compounds.*

(3) *Volume of liquid: there are three regions of the body in which water is found:* extracellular water, *which includes the water in the blood;* interstitial water *or liquid circulating between the cells; and the* intracellular water, *entering into the composition of the cells, which represents 40 per cent of the weight of the body.*

(4) Toxic substances: *endogenous toxins, that is to say, those produced by the organism (urea, ketonic acids), should be differentiated from exogenous toxins introduced into the body. A number of antibiotics are also eliminated in the urine.*



*Figs. 3 and 4. The study of pulmonary ventilation. Above, a spirogram: A. volume of inspiratory reserve: B. tidal air; C. volume of the expiratory reserve: the spiked curve represents the tracing taken with the subject at rest. Below, deep inspiration followed by a forced expiration: 1, maximum expiratory volume per second (MEVS), 2, vital capacity (VC).*

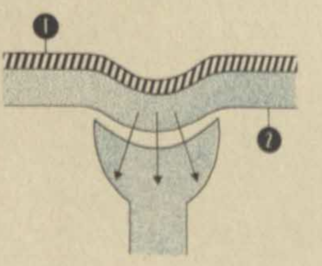


*Fig. 5. Filtration in the nephron: the concentrations are the same in the plasma and in the glomerular filtrate. 1, blood corpuscles; 2, plasma.*

the screen makes it possible to say, when the shadow of the heart is enlarged in volume, which cavity is dilated.

Angiocardiography consists in injecting a radio-opaque substance into the circulation. Radiographs then taken at an accelerated rhythm show the successive fillings of each cavity of the heart and of the vessels.

## *Electrical activity of the heart*

Each contraction of the heart is accompanied by a loss of electric charge from the heart muscle, which is very quickly recovered. The electric currents thus generated can be measured. The tracing obtained gives information especially on the relationships between auricular and ventricular contractions, on the blood supply to the heart muscle, and on hypertrophy of this or that cavity of the heart.

## *Investigation of the functions of the kidney*

The circulation is not a closed circuit. There is at least one pathway open for the excretion of used products. If this did not exist, the organism would progressively poison itself, and this occurs if the excretory channels are closed.

The chief function of the kidney is to eliminate from the body certain substances, water, electrolytes and toxic substances, in order to keep the composition of the internal environment constant and to rid the organism of a certain number of toxins.

Study of the functions of the kidney thus consists of: *(a)* analysis of the different excretory mechanisms; *(b)* analysis of urine composition; *(c)* estimation of the equilibrium of the internal environment.

1. The kidneys' ability to excrete can be precisely stated, thanks to the idea of *clearance*.

The *clearance*[1] of a given substance is the relation between its output in the urine each minute and its concentration in the blood plasma: $C=UV/P$. The volume of plasma completely cleared of the substance $V_{pl}$ is given by the formula $V_{pl}C=UV$, because all of it found in the plasma passes out in the urine. Clearance is thus the volume of plasma cleared of the substance in one minute.

*(a)* If the substance is filtered out in the glomeruli, but is not later reabsorbed or secreted (*inulin*, mannitol), its *clearance* is equal to the glomerular filtration F, because its concentrations in the plasma and in the glomerular fluid respectively are identical: $FP=UV$, $F=UV/P=120$ (fig. 5).

*(b)* If a substance, after it has been filtered out in the glomeruli, is partially reabsorbed in the tubule, its *clearance* C is less than F. In this instance, $F-C$ shows the degree of the reabsorption; this happens with urea: $C=60$ (figs. 6 and 7).

*(c)* If a substance is secreted by the tubule to such a degree that the plasma that leaves the kidney is totally cleared of it (para-amino-hippuric acid), its *clearance* is equal to the volume of plasma that passes through the kidney: $C=700$ (figs. 6 and 7).

Hence one can calculate the volume of glomerular filtrate, the quality of the reabsorption and that of the secretion by the tubules, as well as the renal circulation of blood.

2. Certain investigations give information about both lesions of the kidney and its functions. Examination of the urine is the simplest of these. The presence of albumin or blood in the urine shows the existence of an increase in the permeability of the glomerular filter and therefore of a lesion of the glomeruli.

Intravenous urography[2] is a radiographic examination of the kidney, made after the injection of a radio-opaque substance which is excreted in the urine. Functional insufficiency shows itself by delay in the elimination of this substance. Macroscopic lesions of the kidneys and their excretory ducts are shown on the radiographs.

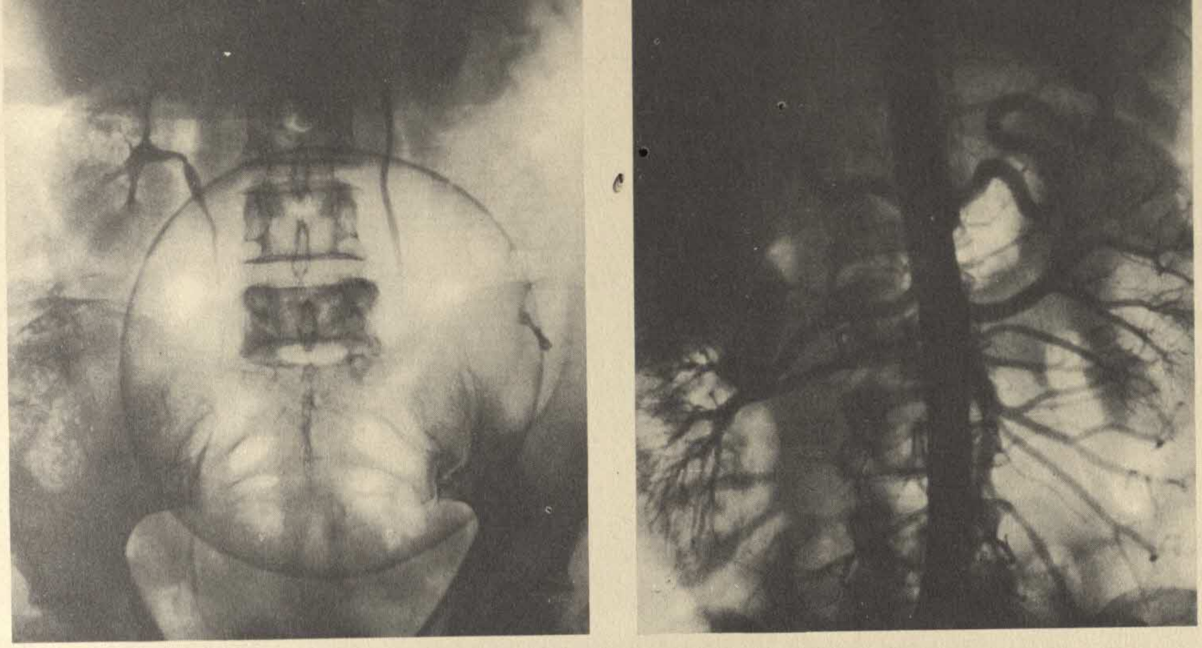
3. By adapting its excretions to its supplies, the kidney keeps the volume and composition of the interstitial fluids of the organism constant, and also the acidity of the blood.

The volume of these fluids can be measured by injecting a substance which becomes diluted in a given area in which fluid is found in the body.[3] Considerable retention of fluid produces oedemas and increase in weight.

The composition of the body fluids is estimated according to the composition of the blood; essentially chlorine, sodium and potassium are estimated, the excretion of which depends on the kidney and is changed in cases of renal insufficiency.

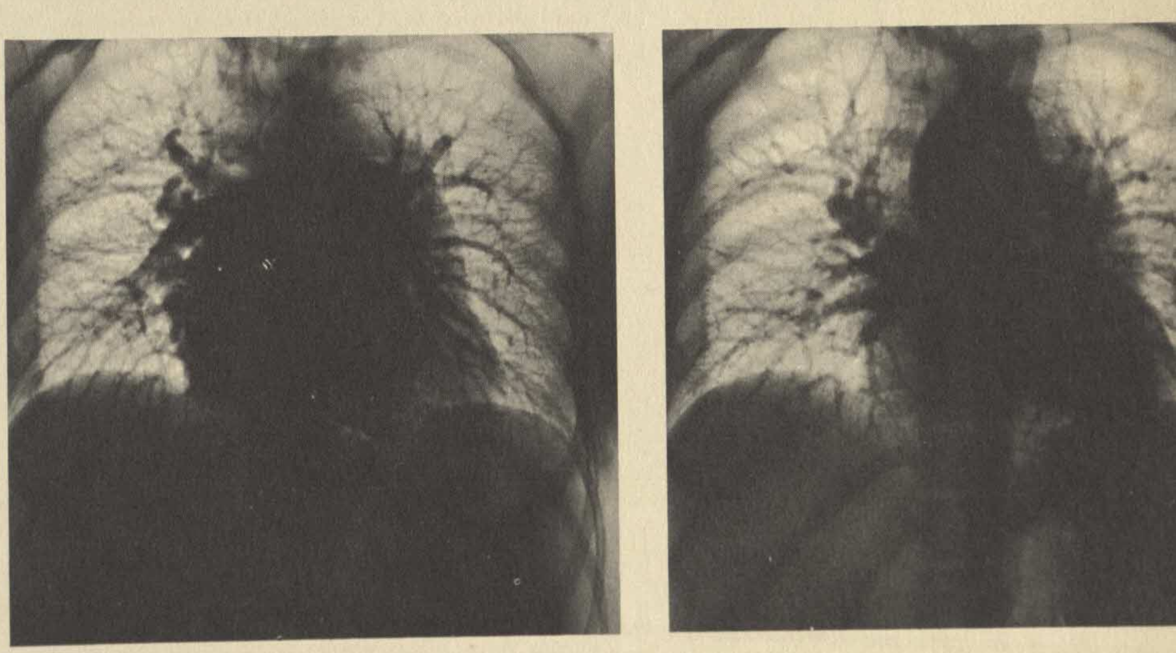
The total acidity of the blood is estimated by determining the pH or by estimating the different acid or alkaline constituents of the blood. The all-important maintenance of the acidity of the blood at a strictly fixed level depends largely on the kidney.

The elimination of toxic substances[4] is exactly assessed: by estimating the urea in the blood, this urea being a waste product of nitrogenous metabolism, the level of which

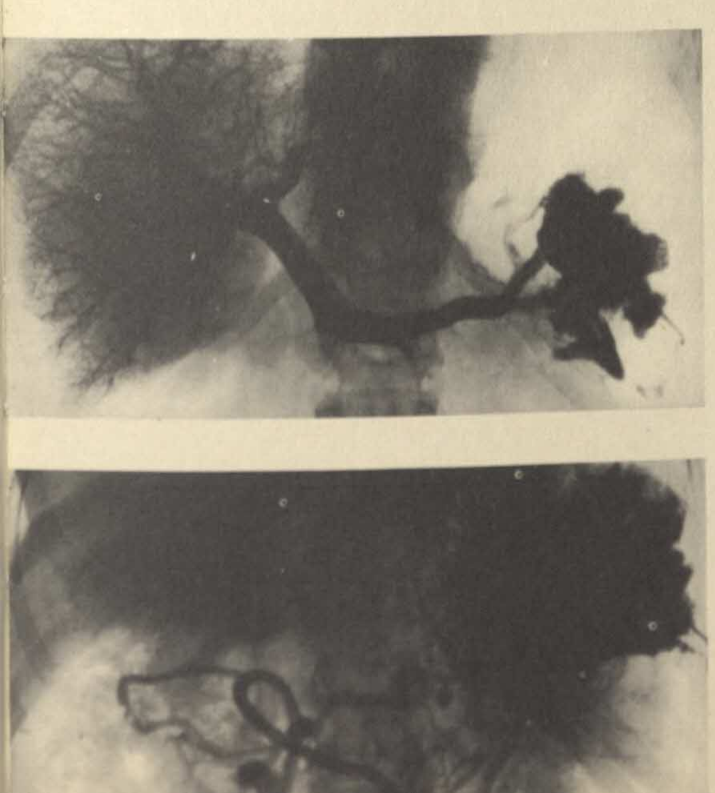


*Physiology of the kidney: opposite, on the left, a normal intravenous urogram. The two kidneys are rendered opaque by an iodized substance, as is the kidney pelvis. The two long, descending bands, which run from the kidneys to the bladder (at the bottom of the picture) are the ureters. The central circular image is due to a balloon which compresses the abdomen. Opposite, on the right, a normal aortogram. The iodized contrast substance fills all the arteries. On this radiograph are seen (in the middle) the descending abdominal aorta, which sends out branches on each side: the two upper branches supply the liver (right) and the spleen (left). The two lower branches supply the kidneys. A lesion of the renal arteries is very easily demonstrated by this method.*

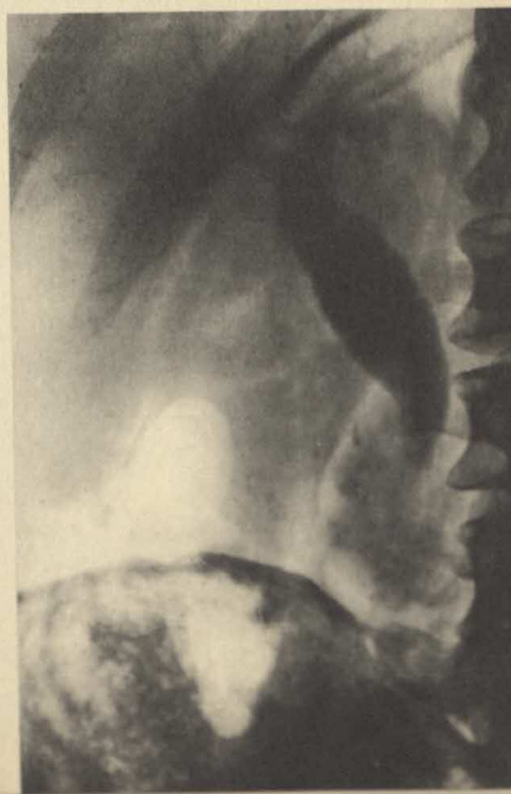
*Physiology of the heart: a normal angiocardiogram. The two photographs show the heart at two different phases of the cardiac cycle: opposite, the contraction of the right side of the heart, in the course of which the right-hand cavities of the heart, the auricle and the ventricle, are made opaque by the opaque liquid, as are also all the branches of the two pulmonary arteries which ramify in the lungs. On the right, the filling of the left side of the heart, in the course of which the left-hand cavities of the heart fill with blood; the large oval opaque area towards the right is the left ventricle, from which the aorta passes out above, its outline being like that of a walking stick curved like a crook, and the abdominal aorta along the vertebral column.*



# *Radiographic investigations*



*Functions of the liver and spleen. The two radiographs on the left are splenoportograms. Above, in a person in good health: on the right of the photograph, the spleen, from which the splenic vein passes, which, just as it enters the liver (on the left) ramifies into branches that become finer and finer and supply the liver cells. Below (left) the splenic vein is obstructed and therefore invisible; it is replaced by secondary veins that more or less adequately take the place of the splenohepatic portal system. The radiograph on the right, which is a cholecystogram, shows the bile duct through which the bile passes out. The gall bladder is not visible, but the outlines of the bile duct, the calibre of which is dilated to three or four times the normal, are clearly visible.*



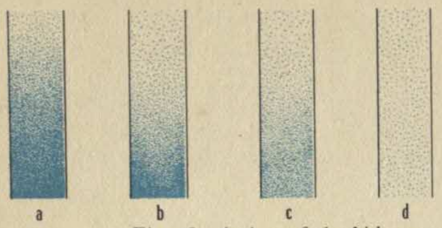


*Fig. 6. Action of the kidney on renal filtration. Depending on the substances present in it, the concentration of the filtrate is more or less high, because of reabsorption into the tubule. A, para-amino-hippuric acid (reabsorption of water by the tubule); b, inulin, simple filtration; c, urea, partial reabsorption; d, glucose (total reabsorption).*

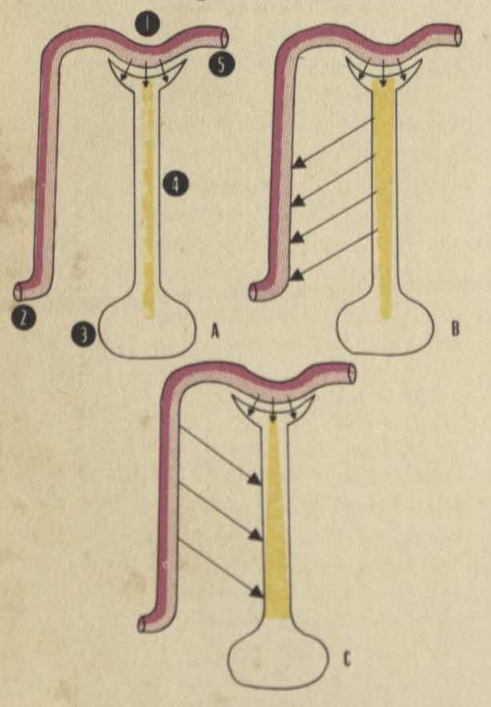


*Fig. 7. Functioning of the kidney with regard to three different substances: A. Inulin, mannitol: glomerular filtration only; B. glomerular filtration followed by reabsorption by the tubules; C. para-amino-hippuric acid: glomerular filtration, followed by secretion by the tubules.*

increases during renal insufficiency; by estimating the amount of a pigment excreted solely by the kidney into the urine in a given time, such as phenol-sulphone-phthalein.

## *Investigation of the functions of the liver*

The kidney eliminates, the liver transforms. The liver is the laboratory of the body. It produces from the chemical substances that are brought to it from the intestine, a very large number of substances; proteins, sugar, lipids (cholesterol), the substances that control coagulation, bile, certain enzymes, etc. Each of these functions can be investigated. By studying them, one can learn whether disturbance of function is due to an inflammation or necrosis of the hepatic cells. By other methods of study, one can investigate the circulation inside the liver, as well as bile secretion.

Synthesis of numerous substances thus takes place in the liver, together with excretion through the bile of certain substances produced in the body or which are foreign to it.

Thus, to investigate the functions of the liver, we can:

(1) measure the blood contents of the substances produced by the liver;

(2) estimate the excretion into the bile of certain substances, or their removal;

(3) investigate biological signs of inflammation or,

(4) of necrosis of the liver.

## *Investigation of the function of synthesis*

The liver synthesizes a large number of substances, the production of which is diminished in hepatic insufficiency: among the most important are protein constituents of the blood; the albumin essential to maintain normal hydration; prothrombin—a factor necessary for clotting and fibrin—and glucose, derived from glycogen stored in the liver and cholesterol.

## *The function of purification and biliary function*

Certain foreign colouring substances are fixed by the cells of the organism and then eliminated in the bile. By injecting a given amount of one of these substances into the blood, its content in the blood falls rapidly as the substance appears in the bile.

If there is hepatic insufficiency, these substances disappear from the blood rather slowly and their appearance in the bile is retarded. Usually, bromo-sulphon-phthalein and rose bengal are used.

Biliary function is measured by estimation of the blood content of the normal constituents of bile (bilirubin, bile salts, cholesterol).

## *Inflammation of the liver*

Inflammation of the liver is accompanied by multiplication in it of cells belonging to the reticulo-endothelial system which synthesize the globulins. This results in an increase in the blood content of the globulins, estimated by electrophoresis,[5] and in instability of the serum, shown by disturbance of the balance of its constituents: this instability causes flocculation of the serum in the presence of certain reagents.

## *Necrosis of the liver*

The destruction of liver cells results in the passage of a certain number of their constituents into the blood and the blood content of these is much increased. This is true of an enzyme (transaminase) and of iron, both of which are especially abundant in the liver cell.

To these purely functional investigations can be added anatomical tests of special interest:

*Cholecystography* or radiography of the bile ducts. These are filled with a substance which is eliminated in the bile and is radio-opaque.

*Splenoportography*, which consists in taking a series of radiographs, after injecting a radio-opaque substance into the spleen. This fluid fills the portal vein and its intrahepatic branches;

*Hepatic gammagraphy*, which is done by injecting into the circulation a radioactive substance which is taken up by the liver, and by then observing the rays emitted by this organ. A map of the liver can thus be obtained. If there is a tumour or a cyst, it reveals itself by an area less radioactive than its surroundings.

*Biopsy of the liver* consists in sampling, by puncture with a needle, a very small fragment of the liver which can then be examined with the microscope. The judicious combination of several of these methods makes it possible to carry out a very precise analysis of lesions of the liver and of their repercussion on the functions of that organ.

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*(5) Electrophoresis makes it possible to separate substances which are fairly closely related, but have different electric charges; paper is soaked with these substances in solution and then put in an electric field; the substances then migrate on the paper, according to their electric charges.*

# Identification of lesions

### *Roger ROBINEAUX and Micheline LEVAME*

Identification of lesions is made on post-mortem[1] or biopsy[2] material which is fixed and embedded in wax (paraffin, beeswax or spermaceti) or frozen; sections of the material are made with the microtome and stained. The examination of preparations is based on different methods of using the optical microscope: polarized light, phase contrast, fluorescence, historadiography, autoradiography, histophotometry. The electron microscope[3] is also used.

Lesions can be classified into three main types: inherited abnormalities; acquired abnormalities, many of which are inflammatory; and neoplastic[4] changes, which are characterized by the development of an autonomous new growth. Many varieties of pathological process are recognized. Those which concern us most here are neoplasms, and it is the recognition of these lesions that we shall discuss. A certain number of morbid processes do not fit into this classification because of our ignorance of their significance.

## *The problem of tumours*

It is not the intention to discuss here the various infective inflammatory lesions (abscesses, tuberculosis or toxic lesions, alcoholic cirrhosis) but to deal with neoplastic affections; these affections present the most distressing problems and in dealing with them it is necessary to make a very careful assessment to serve as a guide for treatment and the forming of a prognosis.

The pathology of tumours is dominated by the problem of cancer. This comprises tissue hyperplasias,[5] which correspond to an exaggeration of the ability of one or several groups of cells to multiply, and neogenesis (neoplasias), which produces benign or malignant tumours.

Tissues are derived embryologically from three layers: ectoderm, mesoderm and endoderm. Ectodermal tissues are the epidermis and its associated sebaceous and sudoriparous glands; from mesoderm are formed the connective tissues, the reticulo-endothelial system comprising the lymph nodes, and the haemopoietic tissues; tissues derived from the endoderm comprise the digestive tract and its offshoots, thyroid, lungs, liver, pancreas, and bladder.

Tumours can be classified according to their embryological origin, but this classification is chiefly of interest from the point of view of tissue differentiation. In diagnostic practice tumours are designated according to their epithelial, connective-tissue, or reticulo-endothelial differentiation. Because these three kinds of tissues are represented in all organs they do not show any topographical exclusiveness. Nevertheless, a type of tumour that is characteristic for each organ can be observed: thus the great majority of gastric tumours are proliferations of epithelium of glandular type. A tumour of uterine muscle is primarily a fibromyoma. A tumour of the breast is, as a general rule, derived primarily from glandular tissue.

Although tumours appear as autonomous proliferations, they can become a disease system of an organ: the first manifestation, for instance, of a leukemia, before the appearance of blood disturbances, is often a lymph gland enlargement.

## *The identification of tumours*

The idea of malignancy clearly dominates the anatomical-pathological diagnosis of tumours.[6]

A proliferation of this kind may develop in the covering surfaces; they then form visible growths that are sometimes peduncular and soon cured. Papillomas, warts and moles come into this category.

When tumours involve a deep tissue they compress and displace adjacent tissues as they grow and usually reveal their existence through secondary evidence of compression. Diagnosis by the pathologist then rests on the known criteria of malignancy. On these criteria a cancerous lesion will be identified as soon as possible after the taking of a sample biopsy.

The criteria are structural and cellular. Their study is necessary whenever the tumour under examination has not revealed its malignancy by a decisive macroscopic feature: the existence of metastases.[7]

The dominant structural feature is the breakdown of the equilibrium between connective and epithelial tissues, the harmony of which governs all organic and benign processes. The result is an anarchy that charac-

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(1) Post-mortem *or* necropsy *means the examination, by dissection, of the organs of a dead body. A post-mortem must be carried out only under very strict conditions and is performed under strict control exclusively for scientific, diagnostic, or therapeutic purposes, the latter being concerned with the use of organs or tissues for grafts, such as bone or corneal grafts. For a long time necropsy was the only method of anatomical examination and was introduced by Morgagni in the sixteenth century.*

(2) Biopsy, *or a sample obtainedby biopsy, is a fragment of tissue taken from a living organ.*

(3) *Optical and* electron *microscopes: see the chapter 'The Techniques of Biological Research' by Philippe Sengel in Volume 1 of* The Living Universe.

(4) Neoplastic changes *are new or autonomous formations of tissue resulting in a superfluous formation or tumour.*

(5) Hyperplasia *means quantitative modifications resulting in an increase in the volume of a tissue.*

(6) *'Benign neoplasms are characterized by their exclusively local, expanding, and not invading growth . . . Malignant neoplasms are characterized by their autonomous, invasive and aggressive growth, which is infiltrating and destructive, and by their tendency to propagate themselves at a distance from their initial site by way of the circulatory system in the form of secondary metastatic tumours' (Masson).*

(7) Metastasis *means a secondary tumour.*

(8) Keratinization *is a form of differentiation of the epider-*

terises the proliferation from its beginning.

The second important structural feature is the infiltration of peripheral tissues. There is no capsule of connective tissue bordering the growth, as in benign proliferations.

Structural differentiation, when it exists, is essential for the diagnosis of the origin of a metastasis; the discovery of a secondary tumour, most often in a lymph node, may be the first step in the analysis of a pathological process; the pathologist must not only confirm or disprove the malignant nature of the tumour, but also do his utmost to determine the type differentiation, its nature, and eventually where it originated; from these data the type of treatment can be worked out. As the microscopic appearances of a tumour are more often than not a poor guide to its source, the diagnosis must be based on a number of clinical and topographical data. The cellular criteria of malignancy are those which show increased ability of the cells to multiply: abundance of mitoses, increased protein synthesis, abnormal forms, autonomy of proliferation (atypical mitoses, voluminous budding nuclei, multiple large nucleoli, disorganization of the normal nucleo-cytoplasmic ratio). The isolated cell may also show differentiation, such as a glandular secretion, or *keratinization*[8], indicating a glandular neoplasia or a tumour of the epidermal type.

Other lesions in the same category are capable of being differently interpreted and do not always reveal their malignant potentialities: they are common to inflammatory and neoplastic processes and are known as *metaplasias*.

## *Pre-cancerous disorders*

'Metaplasia is the transformation of tissue of one kind into that of another.' Thus the epithelium lining the bronchi, normally one layer of cylindrical cells, can become stratified and change to the Malpighian type. This is seen in inflammatory processes, but it also happens in the neighbourhood of cancers of the lung, denoting perhaps a pre-cancerous stage. The type that is best known, because it is the most evident, is leucoplasia of the mouth or of the tongue, which corresponds to the transformation of non-keratinized stratified epithelium into an epithelium with whitish keratinous scales. These modifications, often caused by dental lesions or by smoking, can develop towards malignancy.

The gastric mucosa frequently shows an intestinal metaplasia and the mucosa of the upper part of the cervix of the uterus a transformation of the normally cylindrical epithelium into that of the Malpighian type. But these phenomena are all the more worrying because the type of malignant tumour found in these organs most often takes the form of a metaplasia; cancer of the cervix of the uterus is composed of massive Malpighian lobules; cancer of the stomach presents a distorted appearance of the lining of the intestine; cancers of the bronchus are often formed of poorly differentiated sheets of pleomorphic large polygone cells and are termed epidermoid cells; curiously enough, however, lung tumours composed of the tubular columbar epithelium which characterizes the normal bronchial mucosa are rare.

The identification of metaplasias calls for a vigilant search, by means of repeated biopsies, for a possible malignant neoplasia.

The term cancer *in situ* defines the phase of cancer preceding its phase of invasion and its diagnosis depends on cytological criteria of malignancy, no structural disorder having yet occurred. Consequently, the pathologist must proceed with great care before making such a diagnosis. A specimen taken from the cervix of the uterus will often lead him to suspect cancer. He will only diagnose its pre-invasive nature (also called the zero stage) after he has eliminated the possibility, by cutting further sections or by a new biopsy, that a proliferation is already infiltrating but was not detected by the first biopsy. In addition to their bearing on the treatment of the disease, the identification of *in situ* cancers is an important item in the understanding of their cause.

## *Identification of isolated cells*

It is easy to understand that identification of lesions can be made on the cells of which the tissues are composed. While the histopathologist works on materials obtained by post-mortem examination or operation, the cytopathologist studies cells collected chiefly in organic fluids or living tissues.

Cytological diagnosis consists in the examination either of cells originating in blood or exfoliated epithelial cells or parenchymal cells from glandular organs. We shall now consider what may be found under the following categories: blood and haemopoietic organs, body fluids, secretions and exfoliated cells. To fix and stain these cells, either Pappenheim's[9] or Papanicolaou's[10] method is used.

## *Blood and haematopoietic organs*

The blood, which is a liquid tissue,

*mis. The epidermis is composed of cell layers which change from the deeper to the superficial parts in such a way as to end in fatty, refringent, non-nucleated scales composed of keratin. This kind of differentiation can be seen in pathological processes in the linings of internal organs: it constitutes the substratum, for example, of leucoplasias of the mucosa of the tongue. When it is seen in a tumour of unknown origin, it indicates the epidermal character of the tissue involved.*

(9) Pappenheim's panoptic stain *is applied to air-dried smears. It is a variant of the Romanowsky technique. Two mixtures are used for preparing the Pappenheim stain: those of May Grunwald (methylene blue eosin) and of Romanowsky–Giemsa (azure II eosin, methylene blue and methylene violet) the first being used for fixation with the methyl alcohol that it contains, and as a stain when, after five minutes' contact with the pure solution, an equal volume of water is added to the slide. In Great Britain, the Leishman technique is used, in the United States, the Wright technique. All these stains depend on the use of mixtures that are neutral and stable and soluble in methyl alcohol. These become active after suitable dilution with neutral distilled water.*

(10) Papanicolaou's stain *is of a differential type. It shows up cytoplasmic acidophilia and basophilia: it is called a combined stain because it also stains the cell nuclei. Staining of the cytoplasm is obtained by two staining solutions, Orange G and a mixture of light green, Bismarck brown, and eosin. The nuclei are stained with haematoxylin.*

(11) The haemolytic disease *described by Hayem (1898), by Minkowski (1900) and by Chauffard (1907) is a congenital affection in which twenty-five per cent or more of the red cells have a spherical shape and a decreased resistance. Accelerated destruction of these abnormal red cells by the organism is*

contains red cells, white cells and platelets. It is possible to study these quantitatively and qualitatively. The techniques by which the constituents are counted and measured, together with haemoglobin determination, are the basis of our understanding of anaemia, of excessive numbers of red cells, and of deficiency or excess of white cells. The standard method of counting is to use glass vessels of known volume (those of Malassez or Thomas) after suitable dilution of the blood.

Measurement of the red cells has made it possible to introduce a number of new constants: after centrifugation one can estimate the percentage volume (in a haematocrit) occupied by the red cells in a given volume of blood: by finding the number of red cells per cubic mm and the volume occupied by these red cells in this cubic mm, we can calculate the volume occupied by a single erythrocyte: it is normally 90 cubic microns ($90\mu^3$). This average red cell or erythrocyte volume enables us to define more precisely than by the simple measurement of the diameter of the red cell, our standards of microcytosis, normocytosis, and macrocytosis which form the basis of our classification of anaemia. It is also possible to calculate the thickness of a red cell and to deduce from it a constant of sphericity (the ratio of the thickness to the diameter); thus, in certain haemolytic anaemias,[11] this ratio is increased. After determining the weight of haemoglobin and the number of red cells in a certain unit of volume, one can calculate the weight of haemoglobin per red cell; by means of the weight of haemoglobin and the haematocrit one can also calculate the average concentration of haemoglobin in the red cell; normally this amounts to 34 per cent, but it always decreases in anaemia, of whatever type it may be (hypochromic or hyperchromic).

With the help of these different constants, and after determination of the form and staining properties of the red cells in blood smears, it is possible to define precisely the characteristics of a case of anaemia, to deduce its origin, and to investigate its cause.[12]

In the same way, the number and distribution of the white cells or leucocytes will enable us to define a state of infection, and the characteristics of the distribution will especially indicate a specific infection (suppuration due to pyogenic organisms, with an increase of neutrophil polymorphonuclear cells, salmonellosis with neutropenia, whooping cough with a lymphocytosis, rubella with plasmocytosis, etc). This procedure also enables us to determine a *leukaemic* condition, by the presence of an abnormal proliferation, both quantitative and morphological, of the components of one of the white cell series: granulocytes, lymphocytes, or monocytes. The existence of undifferentiated cells, called leucoblasts, points directly to acute leukaemia. The measurement and cytology of the platelets can easily be estimated and helps the diagnosis of various essentially haemorrhagic troubles.

The study of the blood-forming organs[13] provides information about cytogenesis of the cellular elements of the blood by revealing the processes of hyperplasia, aplasia, and neoplasia, of which it will often have been possible to detect a trace in the peripheral blood.

When specimens of bone marrow are taken from the sternum or the iliac crest, spread on a slide, and fixed and stained, the cells in it can be counted and classified according to their type: granulocytic, erythrocytic, lymphocytic, histiocytic, megakaryocytic, and according to their age in each line of descent. The percentages of the different cells will provide information about variations in their distribution in relation to the normal condition.[14]

By taking a specimen of the marrow with a puncture needle it is possible to determine the features of an anaemia, to discover a cancerous invasion, to detect certain functional aspects (failure of certain elements to mature, such as the erythroblasts and megakaryocytes), and especially to diagnose leukaemia, often suggested by the peripheral blood-count, and to estimate the prognosis of the condition according to the morphological features of the affected cells.

Puncture of a lymph node can yield normal cell elements: lymphocytes, prolymphocytes, lymphoblasts, monocytes, promonocytes, and monoblasts. It may also yield cells that are all alike, which suggests a leukaemic change, and it can reveal the existence of an inflammatory granuloma, that is to say, of elements of the granulocyte series that are normally absent from the gland. The grouping of these elements can indicate the possibility of certain pathological conditions and a careful search should be made for proof of their existance. Thus the existence of neutrophil polymorphonuclears, eosinophils and plasma cells and of hyperplasia of the reticulo-endothelial cells, should lead one to search among these last for anomalies of form and staining reactions. Atypical large reticulum cells, especially when binucleate (the so-called Steinberg's cell), are strongly suggestive of Hodgkin's disease. A simple hyper-

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*compensated for by intense formation of red cells in the haematopoietic marrow. It is a curious fact that the goat normally has spherical erythrocytes.*

(12) *See the chapter on anaemias by Ruggero Cepellini and Claude Jacquillat in the preceding volume,* The Human Machine: Disorders.

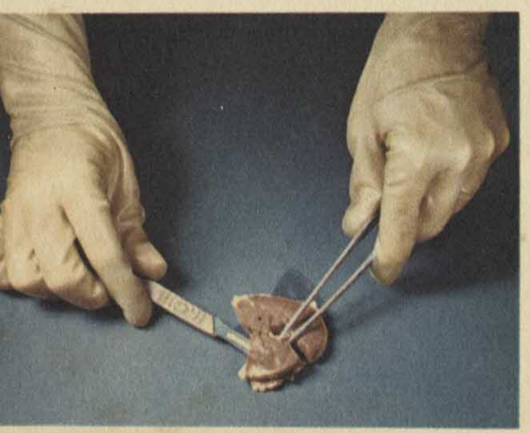
(13) *The system that produces blood and lymph cells has different potentialities and characteristics in different organs: bone marrow, lymph node and spleen. It is formed from a stroma called reticular tissue, composed of fibres arranged in a network in the meshes of which there are reticular cells. These are remarkable elements that have the special biological properties characteristic of the functions of histiocytes: the ability to mobilize themselves, to act as phagocytes, to absorb liquid droplets (pinocytosis), to metabolize numerous substances, etc. The reticular cells can divide and differentiate themselves. They then acquire particular morphological features characteristic of each line differentiated and of each cellular generation in each line.*

(14) *The different pathological aspects of bone marrow can be summarized as follows: erythroblastic marrow (regeneration of red cells); megaloblastic marrow (Biermer's disease); myeloid marrow (infections, myeloid leukaemia); lymphoid marrow (lymphoid leukaemia); monocytic marrow (monocytic leukaemia); plasmocytic marrow (myeloma); neoplastic marrow (cancer); aplastic marrow (leukaemias and poisoning).*

(15) *The spleen can simulate the structure of the bone marrow; this process is known as myeloid metaplasia. Other disorders, either parasitic (eg, kala-azar) or metabolic (eg, Gaucher's disease) can be diagnosed by discovering, in connection with the first, leishmanias, and in connection with the second, the characteristic cells packed with fine crystals of phospholipids.*

# *In a pathological anatomy laboratory*

*To prepare a stained section of an organ for microscopic examination involves a number of operations. In spite of automation, which often helps in the preparation of such sections, it must be the scientist who decides what techniques are to be used and the direction of research. (Photos Lod, taken at the Hôpital Saint-Antoine, Paris, by courtesy of Professor Gosset, with the collaboration of Dr Micheline Levame).*



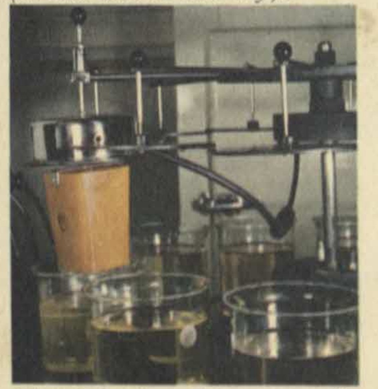
*Removal of the pathological zone, a fragment of tissue, about 3 mm thick.*

*Putting the specimen in a tray that will be placed in a container with similar trays with compartments.*

*This method makes it possible to prepare a large number of anatomical specimens simultaneously (at least three in each tray).*

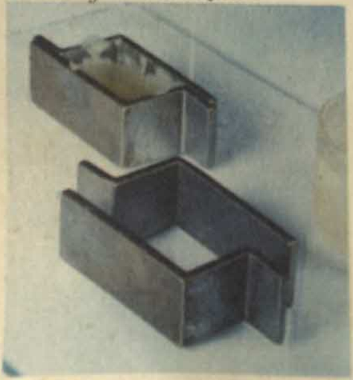
*Each sample must be embedded in paraffin: to do this the container is first attached to a suspending arm.*

*By a combined rotary and up-and-down movement the container is plunged into a number of dehydrating media.*

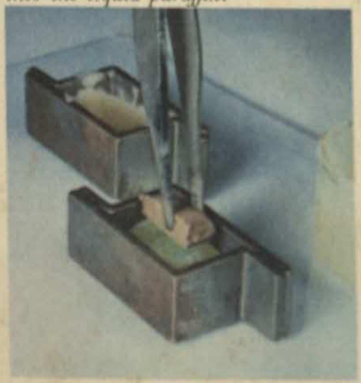


*Then it is plunged into a paraffin solvent. The sample is now ready to be embedded and cut.*

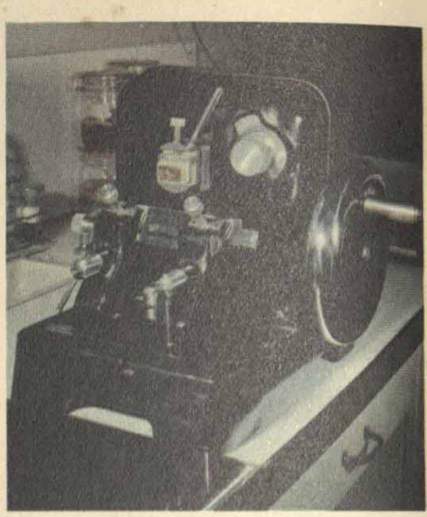
*Leuckhart's embedding boxes, into which the liquid paraffin is run; the boxes can be adapted to make moulds of various sizes.*



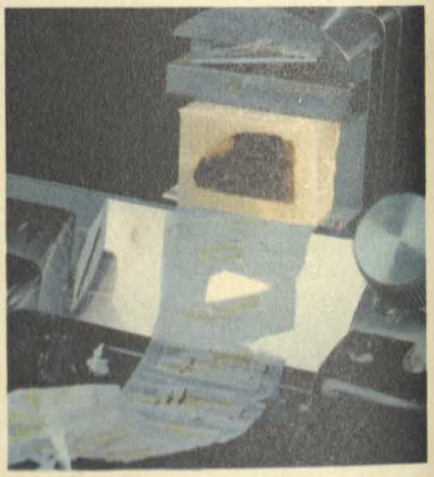
*By the time it leaves the moulding apparatus, the specimen is completely dehydrated and can be put into the liquid paraffin.*



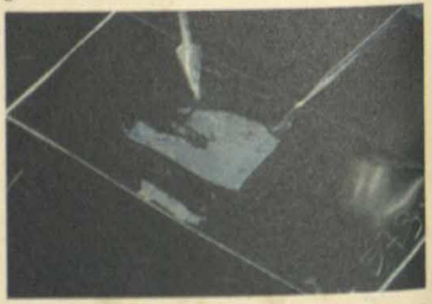
*The block of paraffin with the fragment of the organ embedded in it. Each block is numbered and may be kept for some time.*



*A microtome, an apparatus for cutting the paraffin block into thin sections; the block is held firm by a metal clamp.*



*A ribbon of paraffin sections is cut from the block: its thickness varies from 3 to 5 microns.*



*A piece of the ribbon is spread out and fixed onto a glass slide with gelatin.*

*The slides are put out on trays and dried in an oven before they are stained.*

*The first stage of the staining operation: the paraffin is removed by plunging the slides into a solvent (benzene or toluene). Note the small container divided into compartments which enables the slides to be transferred, ten at a time, from one staining dish to another.*

*The sections are hydrated by successive transfers from absolute alcohol to 70 per cent alcohol and then to water.*

*The technique used here is a triple stain: first, the nuclei are stained blue, by plunging the slides into a bath of haematoxylin (on the left) and then into a bath of lithia water, in which the change to blue takes place.*

*The container filled with slides is plunged into a dish of phloxine, which selectively stains the cytoplasm of the cells red.*

*Each slide is treated directly with alcoholic safranine, which stains the interstitial substances (collagen fibres, for example) yellow.*

*The final phase of the staining. The sections are plunged into toluene or benzene and then covered with a thin glass cover-slip.*

*The cover-slip is applied over the section and affixed with a transparent resin (Canada balsam).*

*The slides are now ready for the pathologist to examine them under the microscope.*

plasia of the reticulo-endothelial tissue and the presence of granulocytes ought to make one think of a virus disease, such as benign reticulosis of inoculation. A puncture may also withdraw pus, and microscopic examination of it may show a micro-organism, for example, a tubercle bacillus.

Puncture of the spleen, which usually gives a mixture of one quarter of polymorphonuclear cells to three quarters of mononuclear cells, most of which are lymphoid, is important in the diagnosis of metaplastic changes.[15]

## *The fluids of the organism*

The normal cells of the blood, polymorphonuclear leucocytes, lymphocytes and mobile connective tissue cells, can be recovered from the normal body fluids and sera of the organism. When these cells are present in body fluids in large numbers we can be sure that an inflammatory or infective condition exists.

The presence of numerous leucocytes and their precise nature in cerebro-spinal fluid enables us to diagnose meningitis and to indicate its possible cause, such as tuberculous meningitis, for example, or a pyogenic meningitis, or again, a meningitis due to a virus.[16]

The same is true of serous effusions, especially pleural effusions. The presence of polymorphonuclears and histiocytes is indicative of an acute pulmonary lesion in contact with the pleura. The presence of lymphocytes suggests tuberculosis. The presence of numerous cells of the pleural endothelium suggests a pleural reaction to cardiac insufficiency. If cancer of the lung is present, a very careful search for neoplastic cells is extremely important, their presence being a contra-indication for surgical removal. It is impossible to exaggerate how difficult the identification of these cells may be, or how easily a simple benign hyperplasia of the pleural endothelium can simulate minor modifications of cancerous cells when they lack the abnormal structure that makes the diagnosis of cancer clear.

## *Secretions and exfoliative cytology*

Most normal or pathological tissues, and especially cancerous ones, can exfoliate, and the cells that detach themselves can be recovered on the surface of the organ (vagina, bronchus), in normal cavities (stomach), or in new formations (cysts). One of the principal aims of exfoliative cytology is the detection of cancer; vaginal cytology also enables us to estimate certain endocrinal functions, because here it is a matter of functional exfoliative cytology.

1. *Search for cancerous cells*

Apart from pleural and peritoneal effusions in which the presence of cancerous cells is a contra-indication for surgical intervention,[17] apart from the demonstration—rare and difficult to interpret—of abnormal cells in the urine, and apart from the discovery—somewhat exceptional—of cancerous cells in the fluid in thyroid cysts, the search for neoplastic cells is most important in bronchial secretions and especially in the secretions of the cervix of the uterus.

In bronchial secretions one can look for cancerous cells directly in the sputum, either in smears or after centrifugation, which leads us back to histology, but it is infinitely preferable to use secretions taken *in situ* by aspiration during bronchoscopy. In fact, positive cases are few. In secretions of the cervix of the uterus this form of examination has, however, become very important. The modifications to look for are those of cancerous cells in general: the large size of the cells, and especially variations between one cell and another; the large size of the nucleus, with an increase of the nucleocytoplasmic ratio and irregularities of the nucleus, which may go as far as being quite abnormal with enlarged and more numerous nucleoli and increased staining properties of the chromatin. These modifications can be found in the Malpighian or glandular cells of the cervix of the uterus,[18] and in the glandular cells or in Malpighian metaplasias of the body of the uterus.[19]

This, of course, is only a rough guide because it may be difficult to differentiate between very slight cancerous modifications and benign hyperplasia. To overcome this difficulty attempts have been made to classify such differentiations. The classification of Papanicolaou and Traut defines five groups:

*Group I:* The absence of abnormal or atypical cells.

*Group II:* The presence of cells that are atypical, but show no structural anomalies.

*Group III:* The presence of suspected abnormal cells, but without sufficient pathological features.

*Group IV:* Cancerous cells in small numbers.

*Group V:* Cells that are clearly cancerous.

Only the last two groups are positive, but the classification of a smear in Group III

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(16) *The cell-content of pathological cerebro-spinal fluid varies; it is almost entirely lymphocytic in tuberculous meningitis, in meningitis caused by viruses (shingles, mumps, poliomyelitis, etc), in icterogenic spirochaetosis and syphilis of the nervous system, and in cerebro-spinal meningitis, due to the meningococcus or other pyogenic causes of meningitis (pneumococcus, streptococcus, staphylococcus, etc). There are abnormal polymorphonuclear cells which multiply in these conditions. In urine the presence of large numbers of leucocytes, whether abnormal or not, single or in masses, or enclosed in cylindrical casts, is conclusive of a diagnosis of pyuria or nephritis.*

(17) *For example, the verification of the presence of cancer cells in a pleural effusion during the development of a tumour of the lung, or of a peritoneal effusion accompanying a mass developed in the liver, is a contra-indication for operation; it shows that the cancerous process has extended to tissues that cannot be surgically removed.*

(18) The cervix of the uterus *is divided into two parts: the inner part includes the canal connecting the cavity of the vagina with that of the uterus and is lined by a simple epithelium rich in glands; the outer part is lined by a Malpighian stratified epithelium, which continues the vaginal epithelium.*

(19) *The cavity of the* body of the uterus *is lined by a simple cylindrical epithelium which covers a vascular connective tissue rich in cells and ground-substance but poor in collagen fibres and without any elastic fibres. The vessels in it have a peculiar structure. The uterine glands are numerous and, like the epithelium, contain a certain number of ciliated cells. The whole of this epithelial and vascular connective tissue undergoes cyclical modifications of endocrine origin.*

(20) Oestrogen activity *is due to the action of folliculine,*

implies the need for further examination: biopsy of the cervix of the uterus or biopsy of the body of the uterus by curettage, according to the results of clinical and cytological examinations.

2. *Functional exfoliative cytology*

The stratified squamous epithelium of the vagina is liable to desquamate under certain conditions related to hormonal activities. At such times one can collect cells with different characters, before puberty, during the period of sexual activity, during pregnancy, and at and after the menopause. It is possible, thanks to Papanicolaou's stain and its variants, to establish percentage curves according to the ability of the cytoplasm of the cells to take up stain (red or bluish green), and according to the size of the nuclei. The spreading-out of the cells or the presence of plications, their grouping in clumps, the elements accompanying them (mucus, erythrocytes, leucocytes, Döderlein's bacilli) are, moreover, differentiating factors of great importance in cytological diagnosis. The normal values having been statistically established, as well as the limits of their variation, it is possible to define cytological criteria of pathological states. Oestrogen activity[20] expresses itself by a predominant desquamation of isolated, large, well spread out polyhedral acidophil cells, with pycnotic nuclei.

The action of progesterone[21] produces a desquamation in plaques. Basophil cells with plicated margins predominate: the size of their nucleus exceeds 5 microns and chromatin is clearly visible.

One can therefore define the phase of ovulation, the phase during which lutein is secreted by a Graafian follicle, and the premenstrual phase of a normal cycle and the states of hormonal deficiency and those of relative or absolute over-production of folliculin and of progesterone. During pregnancy, for example, the excess of secretion of progesterone causes the formation of cells called navicular cells; a threat of abortion can be detected by the reappearance of an important degree of oestrogen activity which will be shown by the presence of large acidophilic pycnotic cells.

## *Frozen section*

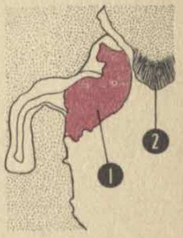
This is a common and rapid procedure, involving the rapid examination of a specimen taken from a lesion during an operation. It makes it possible to synchronize diagnosis and appropriate surgical treatment. Its chief application is to the treatment of cancer of the breast, in which case it acts as a guide in determining the procedure in the light of the spread of the cancer to the lymph nodes. In the same way, cancer of the cervix benefits from rapid examination of the lymph nodes of this region, so that complete surgical removal can be undertaken.

Frozen section is largely used in thoracic surgery: its value is all the greater because the pathology of the thorax is particularly prone to inflammatory lesions which simulate tumours (abscesses, tuberculosis, mycoses, granulomas due to foreign bodies). Pre-operative diagnosis also makes it possible to determine the actual limits of a tumour, the macroscopic aspect of which often gives rise to confusion with contingent inflammatory reactions.

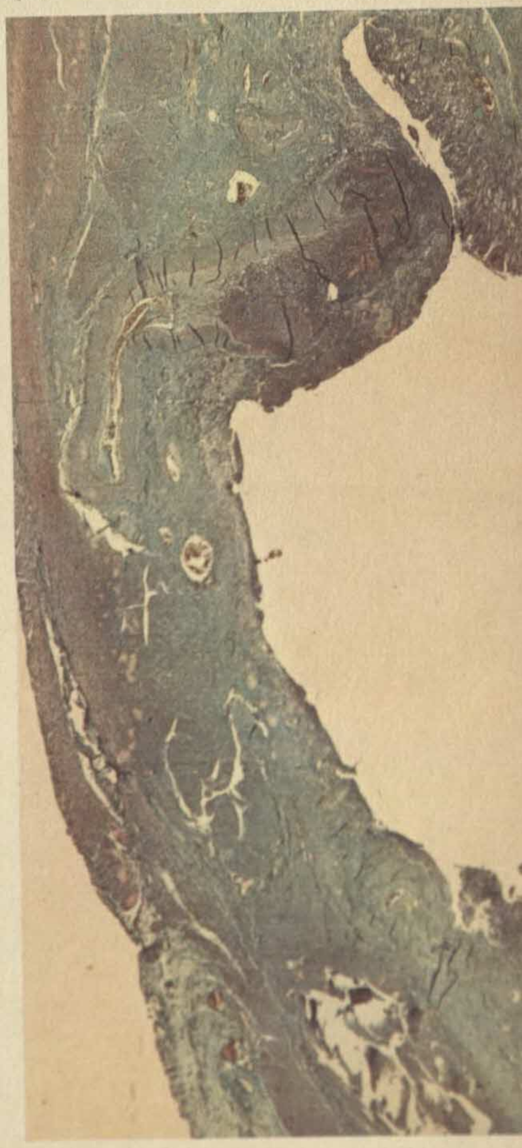
In gastro-enterology the application of this method is limited. Nevertheless, it is possible to distinguish a purely inflammatory lesion in the digestive mucosa from a neoplastic infiltration.

In dermatology frozen section is exceptional, for such diagnosis is almost always made on the histological appearance of samples of tissue subjected to deferred examination.

These, then, are some of the possibilities offered by histology and cytology for the identification of lesions. We have considered only classical techniques. But there are new techniques the development of which has made numerous other practical applications possible. Tissue and organ culture, which maintains the growth of living tissue in a semi-synthetic medium, is widely used in virology, in the study of cancer, and in genetics. The microscopic methods of examining living specimens, employed together with cinematograph film, make it possible to telescope the time-axis[22] and by speeding up the film to demonstrate the existence of pathological phenomena in cells that proceed too slowly to be perceived by the eye. Recent methods of electron microscopy may give reasons for hope regarding the understanding of the ultrastructure of cells and of pathological tissues. These new methods result from a variety of factors—fixatives which act very rapidly and are adapted to the object being studied, and to the use of new embedding media (Perspex, Araldite), the perfecting of methods of cutting ultrafine sections, the use of metallic salts as contrast media (lead, uranium). The morphological identification of chemical disorders at the molecular level is now a possibility.



*Gastric ulcer: there is a patent artery in the floor of this ulcer, which has been occluded by a thrombus taken from the patient shown on page 8. In the diagram: 1, thrombosis; 2, overhanging lip of the ulcer.*



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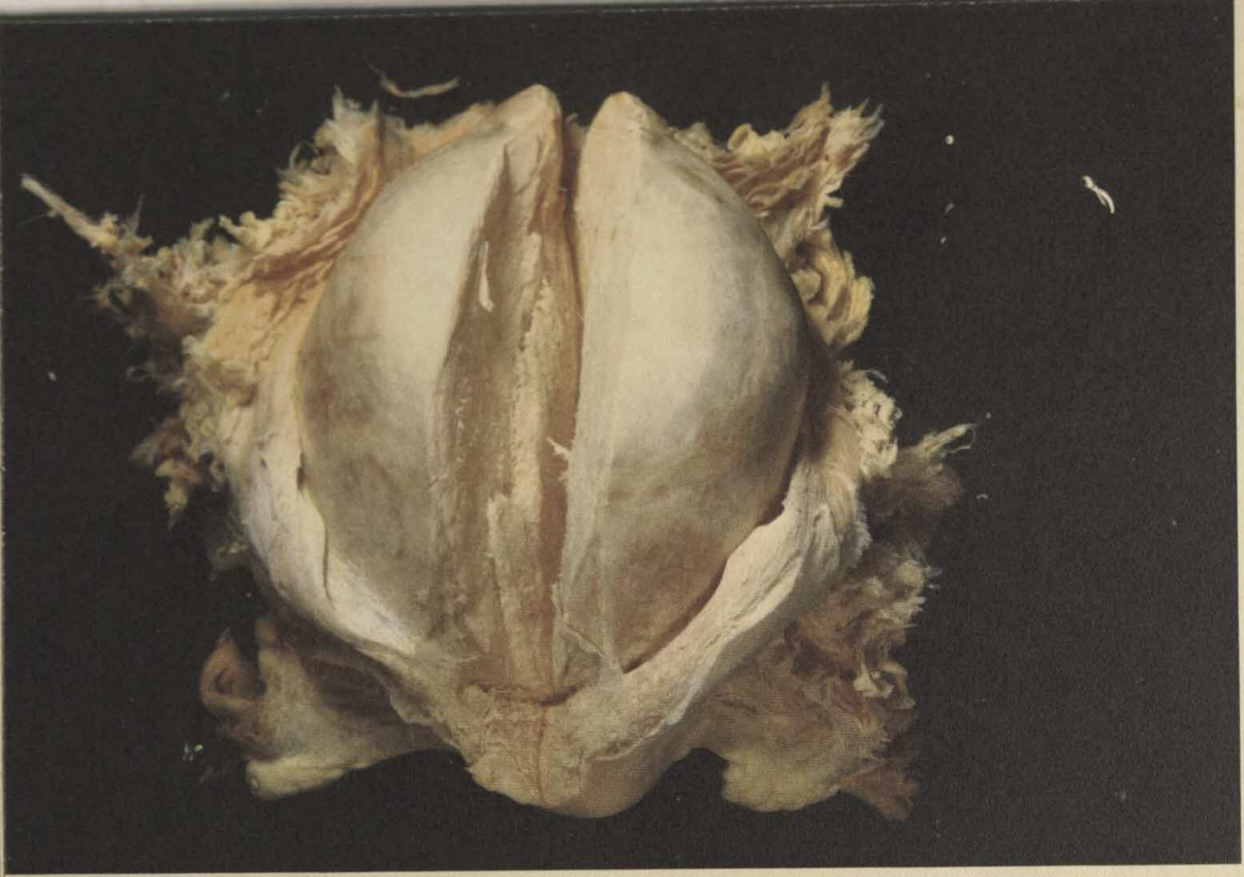
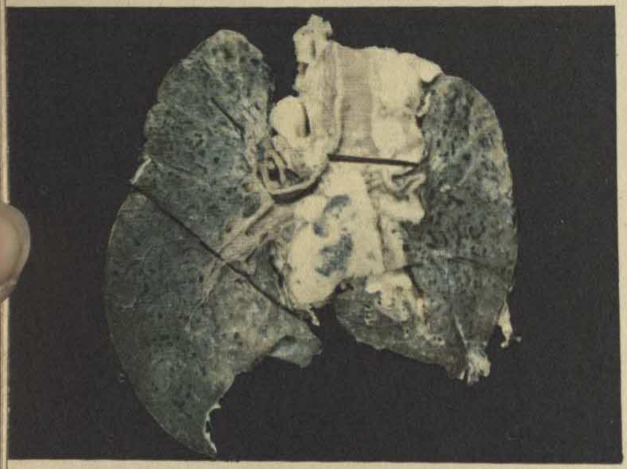
*secreted by the ovary (stimulated by the pituitary) on the mucosa of the uterus.*

(21) Progesterone *is the internal secretion produced by the corpus luteum after stimulation by the pituitary.*

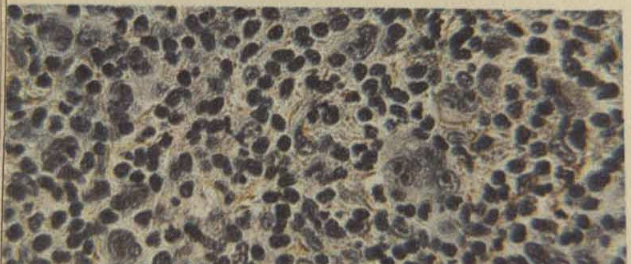
(22) *Film records are usually made and projected at 24 images per second. If one records a movement at one image per second and projects it at 24 images per second, the recorded phenomenon will be accelerated 24 times and thus the time will be shortened.*



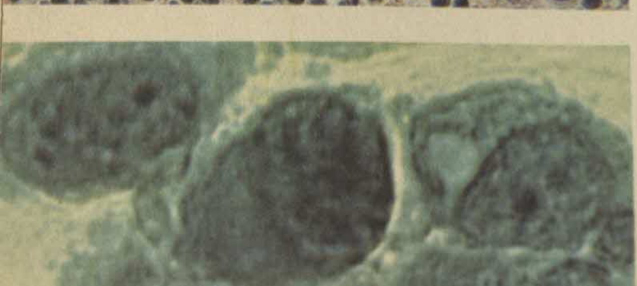
Specimen removed by operation: *a voluminous fibroma of the uterus in the cavity of the uterus: its encapsulation and regular outline suggest that it is benign.*



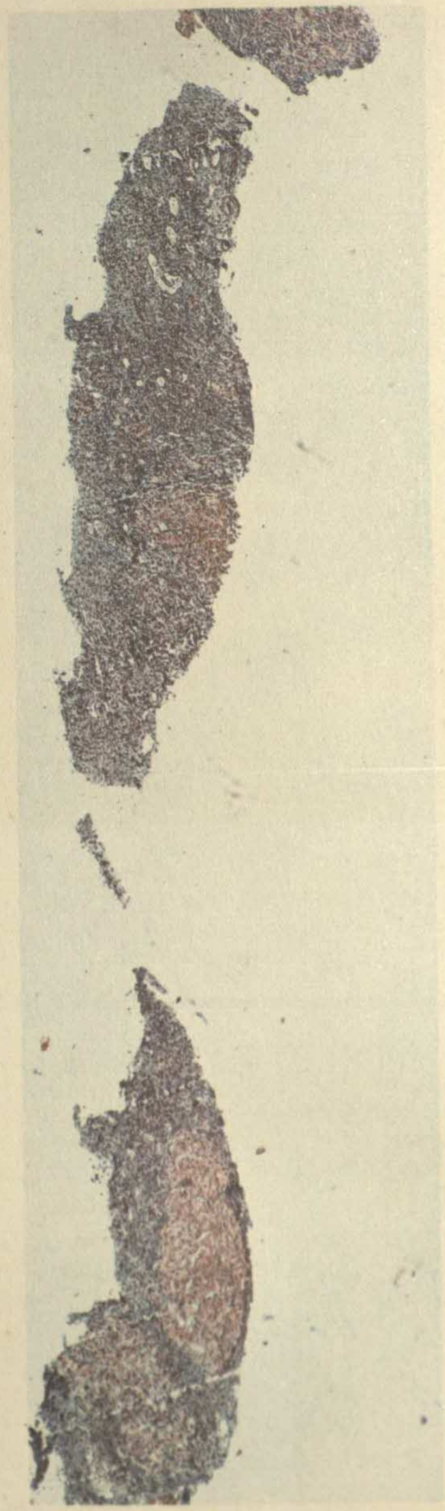
Specimen taken at necropsy *to verify the nature of the tumour: frontal section of two lungs, revealing a malignant neoplastic infiltration of the mediastinum and right lung (on the right). Note traces of the removal of samples for histological study.*



Histological sections: *lymph node affected by malignant lymphogranulomatosis or Hodgkin's disease. The characteristic elements are represented by cells with many multilobed nuclei.*

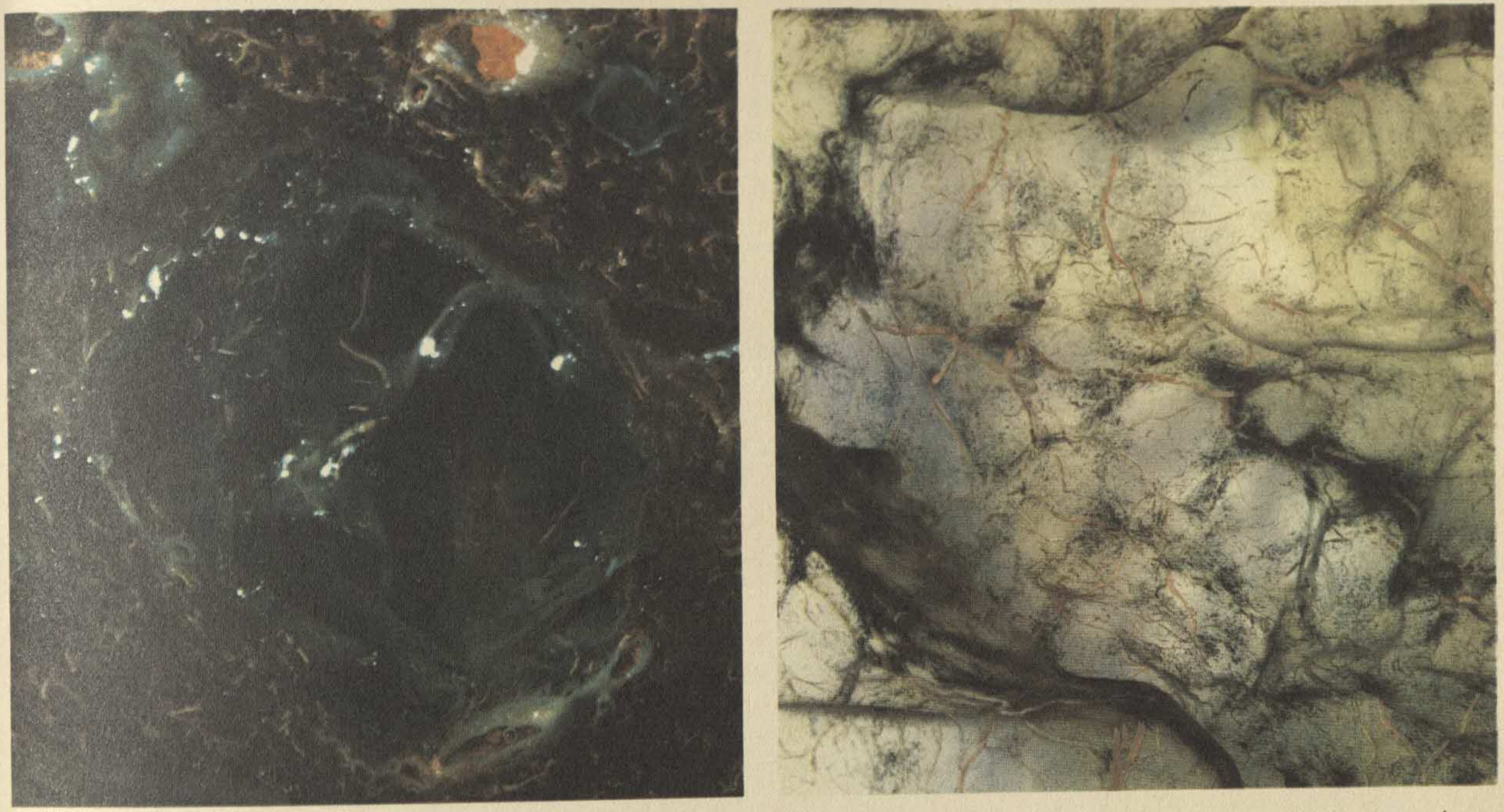


Vaginal smear: *neoplastic cells the malignancy of which is shown by the increased size of the nucleus and the basophilia of the cytoplasm.*



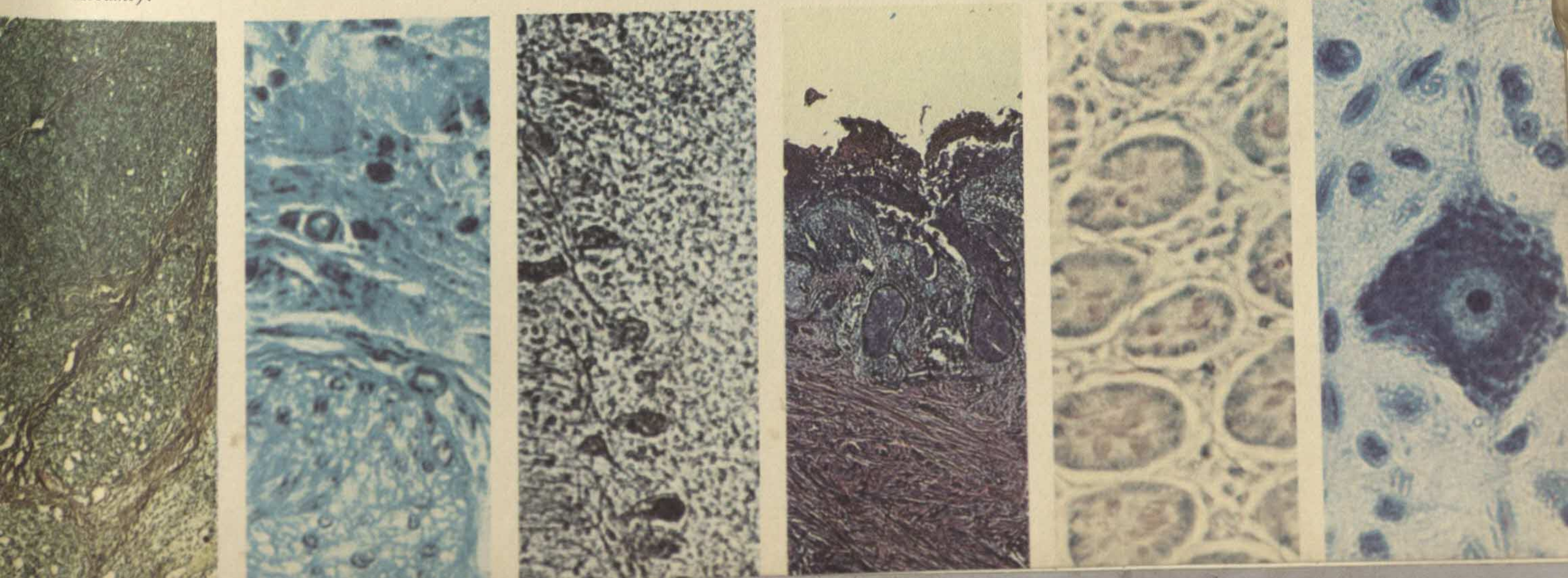
Biopsy by liver puncture: *fragments of liver removed by a special needle passed through the abdominal wall are irregular and small in size; histological examination suggests a diagnosis of cirrhosis.*

# *Some identification techniques*



Special techniques: *the injection of opaque material into the vascular system of an emphysematous bulla: the material used is a suspension of minium-gelatine, which has the advantage that it is opaque to x-rays and can also be located in histological sections. The illustration on the left shows a view of the whole septate bulla. The illustration on the right shows the vascularization in detail. (Illustrations by courtesy of Dr Verley, Hôpital Saint-Antoine, Paris).*

Special histological staining: (a) *picropolychrome, a method of staining which makes possible the differentiation of types of collagen fibres: adult fibres are coloured red, the immature fibres pale blue;* (b) *triple stain with methyl green: a method which shows up the fibrillar structures of connective tissue, causing it to appear green:* (c) *silver impregnations of a section of the cerebellum;* (d) *triple stain with Masson's aniline blue: a method which shows collagen tissue coloured blue;* (e) *staining of the normal mucosa of the colon with Mayer's mucicarmine: vivid red coloration of the mucus at the apical poles of the cells;* (f) *staining with Nissl's blue to show Nissl's granules inside a nerve cell. (Photos Lod, at the Hôpital Saint-Antoine, Paris, with the collaboration of Dr Micheline Levame).*



# Bacteriological research

René PIERON

*The human body is often the victim of infectious diseases caused by its being penetrated by pathogenic organisms. The aim of bacteriological research is to confirm or refute the diagnosis of such diseases. To do this bacteriologists use numerous techniques: some aim at isolating the micro-organism from a pathological product (pus, sputum); others detect serological or cutaneous reactions provoked in the body by the pathogenic agent. Tuberculosis shows that, contrary to current views, the diagnostic or therapeutic problems involved are not always simple.*

It was the German bacteriologist Robert Koch (1882) who discovered the cause of tuberculosis, the tuberculosis bacillus or *Mycobacterium tuberculosis.*

Only by demonstrating the presence of this bacillus can it be affirmed that a morbid condition has a tubercular origin; nevertheless, certain radiological images in the lungs can hardly indicate anything other than tuberculosis even when the most delicate methods of detecting the bacillus give negative results. In any case, scrupulous search for the bacillus must be made; although tuberculosis is no longer a serious threat to life, thanks to the effects of antibiotics, it is still essential for medical and social services to provide prolonged treatment.

The ways in which the pathogenic agent can be detected vary according to the nature and number of bacteria in the pathological product to be examined. Detection depends on three complementary methods; microscopic examination, the culture of bacteria, and guinea-pig inoculation.

## *The detection of bacilli*

Microscopic examination is made with an ordinary optical microscope on smears on slides usually stained by the Ziehl-Neelsen method.[1] Direct examination is often sufficient for sputum rich in discharged tubercle bacilli. In less advanced forms of tuberculosis this examination is negative and standardization of sputum[2] is then necessary, and if need be, more elaborate methods, such as culture and guinea-pig inoculation: examination can also be made of fluid obtained by gastric lavage. The bronchial secretions of patients, particularly women and children who do not know how to spit, and the secretions from the air passages produced during sleep, accumulate in the stomach.

This microscopic examination, though apparently simple, takes a long time and is not reliable because if it is negative tuberculosis cannot be excluded without taking the further step of culture and inoculation. There may also be causes of error: tubercle bacilli may adhere to a slide not properly washed after a previous examination. Also, microscopic detection of bacilli resistant to acid and alcohol is not a certain proof of their being tubercle bacilli; this has to be verified by culture and animal inoculation. The bacilli may be paratubercular. These are widely distributed and are to be found, for instance, in taps and water pipes. It has been observed in recent years that between them, certain organisms, called atypical mycobacteria, are very occasionally the cause of pulmonary diseases in man and can be confused with tuberculosis. Classification of atypical bacilli and study of the criteria[3] for distinguishing these organisms from each other and from true tubercle bacilli has been the object of recent research, notably by Runyon.

When the tubercle bacillus has been identified, the next step is to cultivate it. This is a slow process and may take anything between twelve and twenty days; or it may take even longer, so that a negative finding cannot be arrived at for about two months. The decision is often a difficult one. If tuberculosis is suspected, and if direct examination and examination of a standardized specimen are negative, it will then be necessary to make several cultures before starting treatment, though this must be begun immediately without waiting for the results of the cultures. But certain precautions must be taken; although fluids recovered under sterile conditions, such as those taken from patients with pleurisy, can be cultured directly, pathological products such as sputum specimens, should first be freed from other bacteria.[4]

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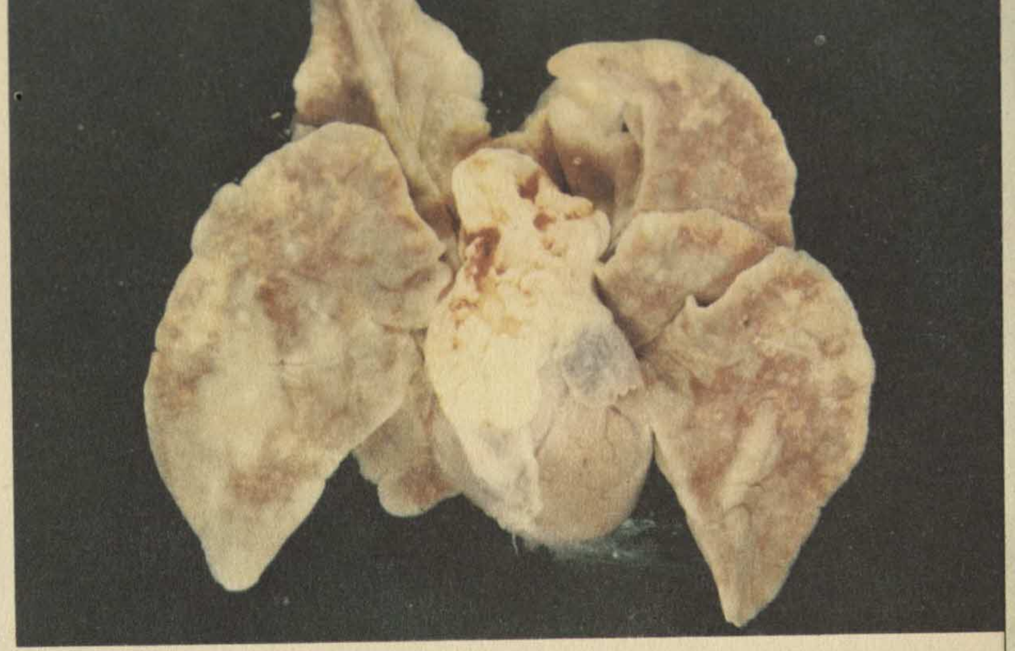
*(1) The Ziehl–Neelsen stain is based on a fundamental property of the tubercle bacillus discovered by Ehrlich: it is resistant to acid and alcohol. When the bacillary structures have taken up the stain, they cannot be decolorized, as other bacteria can, by the action of either acids or alcohol. The Ziehl–Neelsen stain can also be used for the detection of tubercle bacilli in histological preparations of pathological tissue specimens taken by surgery or post-mortem examination.*

*(2) The structure of sputum is not homogeneous. Sample specimens that are to be examined may contain no bacilli, although they are present in neighbouring samples. Standardization of specimen samples equalizes the chances of finding bacilli in different parts of the sputum in specimens that are poor in bacilli. It makes it possible to find them three or four times more often than simple direct examination. The technique of standardization is chosen according to the size of the sample (sputum or fluid obtained by a stomach wash), and according to whether a culture is to be made at the same time or not, this determining whether the specimen may or may not be boiled.*

*(3) Among these critera are the characteristics of the cultures, the distinctive features of the metabolism of the bacilli, serological tests, the inoculation of laboratory animals, and the behaviour of the bacilli in culture in the presence of anti-tuberculous antibiotics.*

*(4) Associated bacteria can be destroyed by various means that do not affect the vitality of the tubercle bacilli. The methods most often used are those of Hohn-Loewenstein, in which sulphuric acid is used, or more*

1



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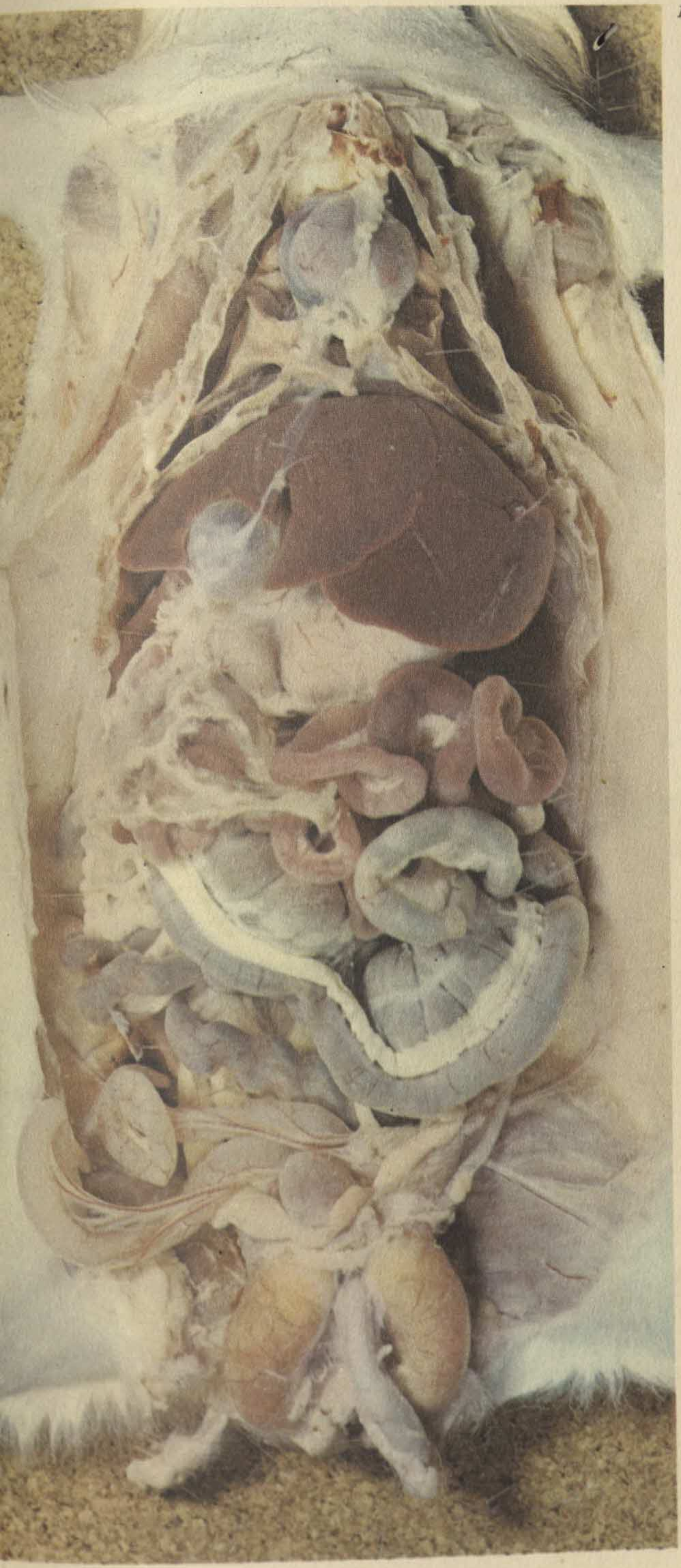

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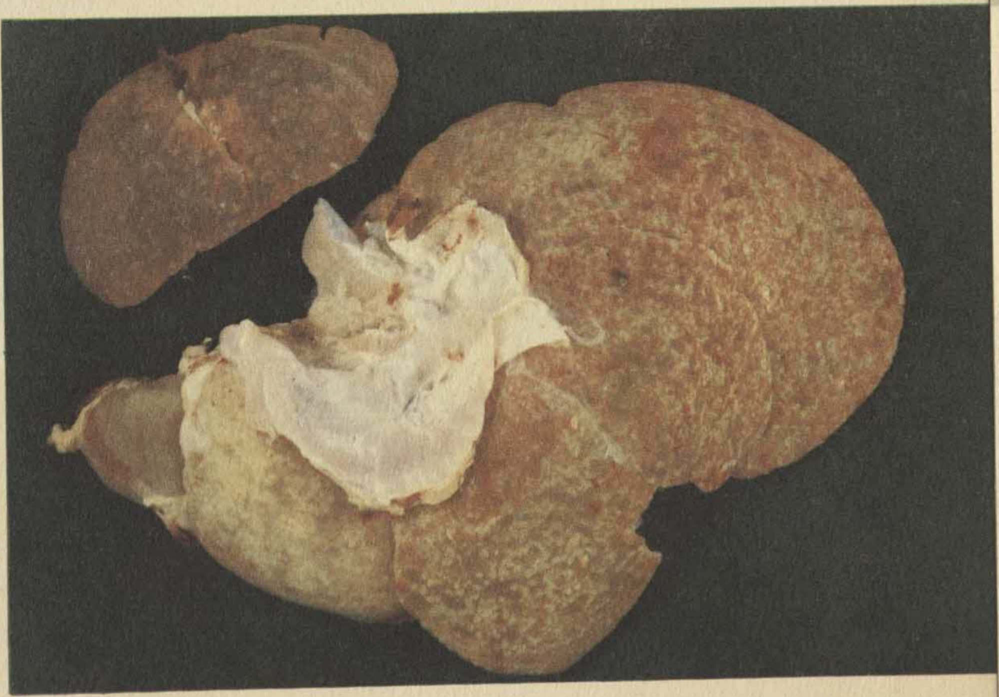

# *Detection of the tubercle bacillus*

*1. Lungs and heart of a guinea-pig after inoculation with material containing Koch's bacilli; note—on the lung—the disseminated white spots with irregular outlines, which are more or less confluent; these correspond to tuberculous lesions;*
*2. Normal guinea-pig;*
*3. Dissemination of tuberculous granulations in the spleen and liver of an inoculated guinea-pig;*
*4. Swollen lymph node in an inoculated guinea-pig.*

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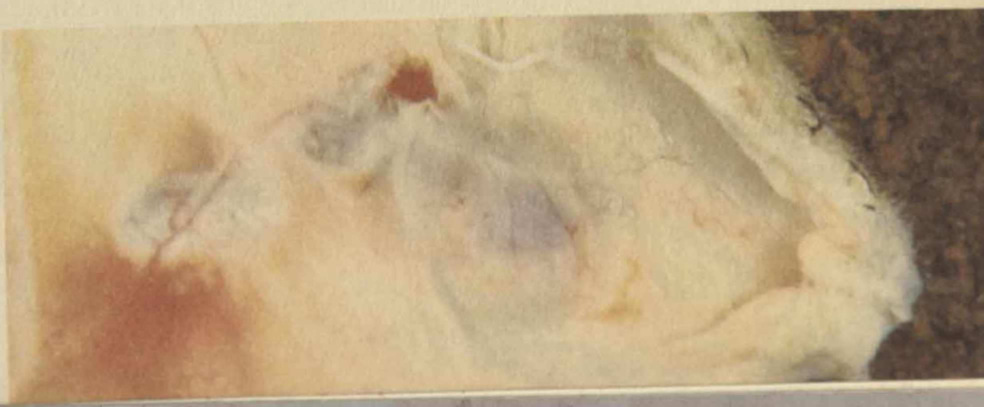
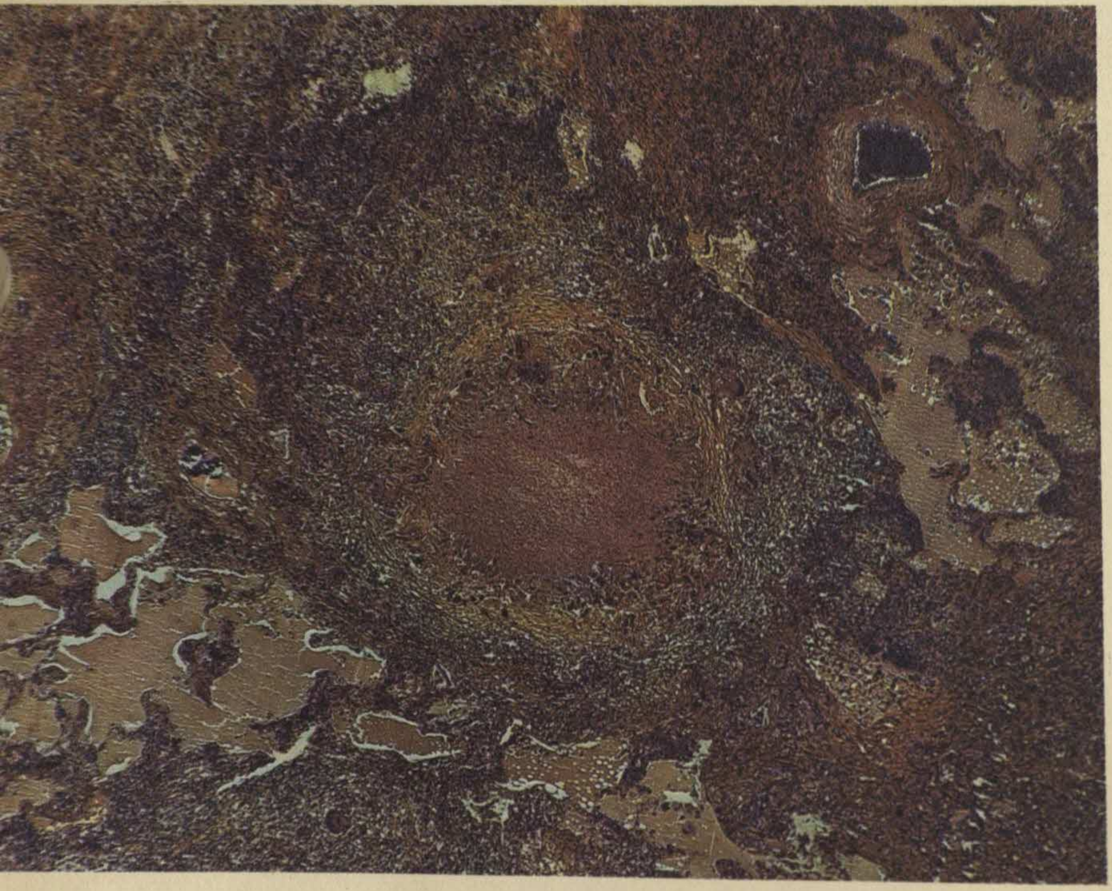


The metabolic needs of human and bovine tubercle bacilli are not altogether identical, so it is possible to determine whether a strain isolated from a pathological product is of human or of bovine origin by the aspect of the cultures, and also by animal inoculation. For the human bacillus, the guinea-pig is the one chosen, for the bovine bacillus it is the rabbit. This distinction is not without epidemiological interest in certain areas in which the bovine bacillus in the milk of tuberculous cattle can cause human tuberculosis.

The composition of culture media includes organic or mineral substances that are indispensable to the growth of the bacillus or favour or inhibit its growth. Among the numerous media that have been suggested are isolation media, used for the detection of bacilli derived from pathological products, and maintenance media used for the conservation or the biological study of strains. The isolation medium most commonly used is a solid medium, such as that of Loewenstein and Jensen, or Herrold's egg-yolk and glycerine medium. Maintenance media are generally liquid; those most used are the albuminous synthetic media of Dubos and of Youmans.

*Tuberculous follicle in the fibrocaseous stage. The finely granulated centre is made up of caseous material. The peripheral fibrillar zone corresponds to scarred fibrous tissue; between the two zones can be seen giant cells and cells of connective-tissue origin that show the development of the lesion. (Photo Lod).*



Detection of the tubercle bacillus by animal inoculation is as sensitive or slightly more sensitive than detection by cultivation. Pathological products are inoculated just as they are, provided that secondary bacteria are first destroyed; but if fragments of an organ are used, they must first be ground up under sterile conditions.

The guinea-pig is inoculated under the skin of the groin. After a week or two, or possibly longer, if the product contains only a small number of bacilli, and if their virulence is low, an adenopathy[5] appears in the inoculated area. This becomes an abcess which, after three weeks or more, opens through the skin.

It is not necessary to wait for this opening in order to prove the existence of tuberculosis; as soon as the adenopathy appears, the animal can be destroyed and a search made for dissemination of swellings and for lesions of the spleen. Samples are taken from these organs, notably from the group of inguinal lymph glands, in order to look for the bacilli, by making smears for microscopic examination after they have been stained, or by grinding up the tissues and making cultures. This precaution is necessary because the syringe used for the inoculation may have contained dead bacilli left over from a previous experiment and which may be found in the smears. Instead of killing the animal, it is possible and simpler to investigate its cutaneous sensitivity to tuberculin[6] by means of the intradermal reaction, a positive result[7] to which appears at the same time as the adenopathy. It is essential that before inoculation of the animal a negative reaction to tuberculin should have been obtained.

If the experimental tuberculosis of the guinea-pig is allowed to develop, the animal will die in a few weeks or a few months and will show massive, characteristic lesions: a hard mass, riddled with abscesses in the inoculated area, adenopathies near the aorta, trachea and bronchi, with caseous degeneration[8] of lymphatic tissue, and nodules and granulomas in the viscera, especially the spleen and the liver, and also in the lungs.

## *The resistance of micro-organisms to antibiotics*

In spite of the discovery of new drugs,[9] the problem of the resistance of the tubercle bacillus to antibiotics is still of great importance. Among patients with tuberculosis of the

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*especially that of Petroff, in which soda is used, although soda is not absolutely free from action on the Koch bacillus; the associated bacteria can also be destroyed with penicillin.*

(5) Adenopathy: *a swelling of the lymph glands or nodes.*

(6) *Tuberculin in a sterile fluid containing the toxins produced by the tubercle bacillus. It is used to test the cutaneous reaction.*

(7) *Cutaneous reactions with tuberculin are negative so long as the organism remains free from all infection by the tubercle bacillus. A positive reaction in man enables us to say only that the bacilli have entered the organism, but not to conclude that the disease observed is active tuberculosis. It is possible to say this only if one is certain that preceding tuberculin tests, made a little earlier, were negative; one can then say that the first*

lung undergoing special treatment and expectorating bacilli, 20 to 30 per cent (almost always patients who have already been treated) have bacilli that are resistant to one or even to several drugs, and very often there is resistance even to the most active of these, isoniazid. Even among patients who have never been treated, resistance is found in 2 to 5 per cent of cases. This, together with fibrous changes in old lesions, is one of the reasons why treatment sometimes fails. It is also a cause of relapses and of their gravity.

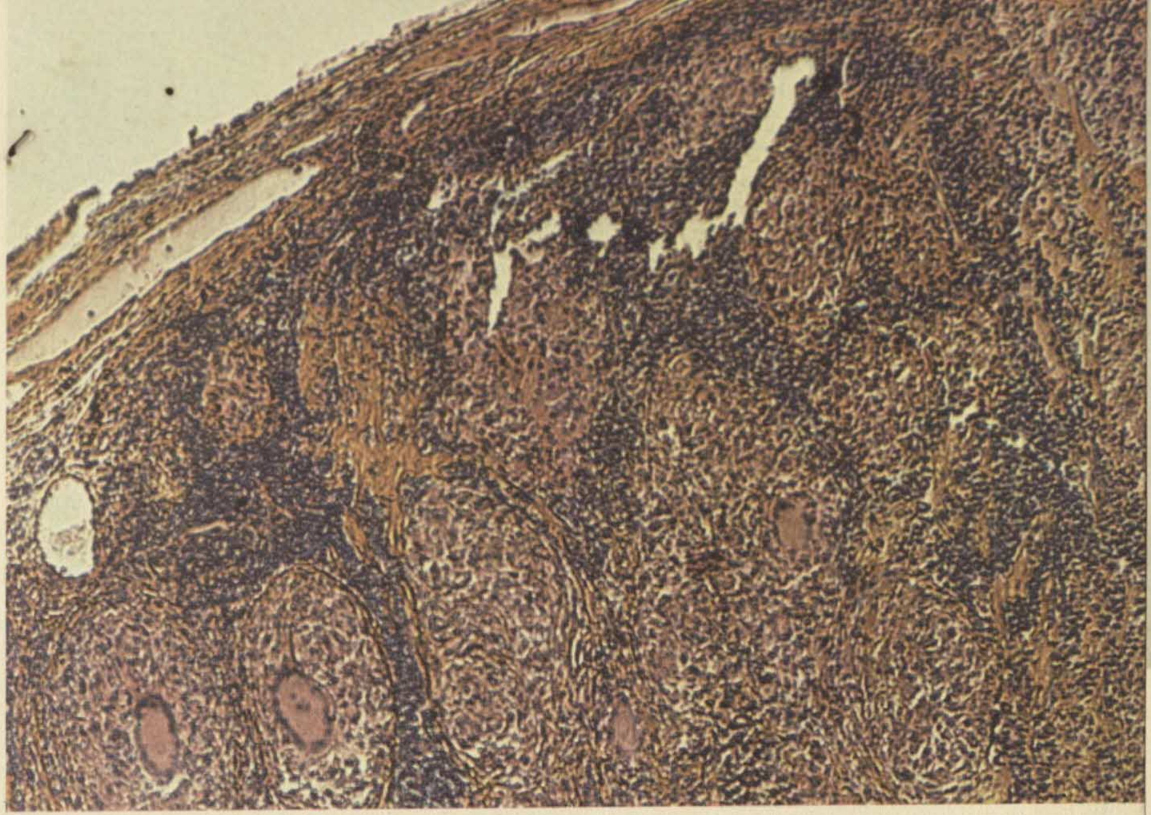
Measurement of the resistance of a strain of the tuberculosis bacillus is made by estimating its development in a culture in the presence of an increasing amount of each antibiotic in comparison with control cultures inoculated with a known sensitive strain. Measurement can be made directly by spreading the pathological product containing the test bacilli on a solid medium impregnated with the antibiotic that is being investigated, after elimination of secondary bacteria. This simple and relatively rapid technique gives results only with products that are rich in bacilli. Measurement can also be made indirectly in a liquid medium to which the antibiotic has been added, by means of a culture of bacilli which has been already isolated. The results can be read by comparing its transparency with that of control cultures; but it is much better to carry out this test also on a solid medium, with more precise results.

Having determined *in vitro* resistance, we are still faced with the problem of its clinical significance in man. This problem has given rise to divergent opinions. To begin with, it was thought sufficient to indicate a level of total resistance corresponding to the lowest antibiotic concentration that will inhibit the culture. If an entire bacillary population resists an antibiotic, there is no hope of that antibiotic being effective; but if only a small proportion of the population resists, the antibiotic will act on the bacilli that remain sensitive to it, and the body, by means of its own defences, will break down the resistance of the others. The precise measurements made on solid media result from the fact that it is possible, provided that the inoculations have not been too numerous (the quantity of the bacilli used must be known exactly and must be as constant as possible), to count the colonies that have been able to grow and consequently to determine the proportions of resistant bacilli.

Another difficulty arises from the fact that it cannot be known whether a lesion is rich or poor in bacilli, and it could happen that most of the bacilli are resistant and the body may not always be able to conquer them.

A third difficulty arises from the fact that although the concentrations of the antibiotic in the cultures used for measuring resistance are known, the concentration in the tissues is not known. The concentration in the blood, which can also be measured, is only a slight indication. Consequently, it is very difficult to fix a critical threshold of *in vitro* resistance that will be valid for all patients and will enable one to be sure that an antibiotic will have no therapeutic action. In practice, it can be said that if the *in vitro* resistance to an antibiotic is strong, there is a likelihood that its therapeutic action will be nil.

If resistance to an antibiotic is weak, its action may persist, but it is handicapped, and in such a case the results of treatment will not be as good as if the cultured bacilli had been completely sensitive. In practice, the measurement of resistance takes several weeks. One cannot, however, wait for the result before beginning treatment. One therefore has to prescribe a mixture of drugs, including the most active ones, isoniazid and ethioniamide, and modify the treatment according to the results of measurement of resistance, as well as the clinical results, the mixture of antibiotics being intended to anticipate the risk of resistance, the manifestations of which would soon appear if only one antibiotic were given at a time.



*A lymph gland attacked by Besnier–Baeck–Schaumann's disease, which shows marked histological analogies to tuberculous lesions: the differential diagnosis is based essentially on the absence of caseous material from the centre of the follicles.* (*Photo Lod*).

*contact with the bacillus has just occurred; it is a primary infection; most often it expresses itself only by the change in tuberculin tests, without any clinical manifestations.*

(8) *Caseous material is a particular substance which results from the destruction of normal tissues by the action of tubercle bacilli.*

(9) *Certain drugs, especially isoniazid (1952), which appeared after the discovery of streptomycin by Waksman (1944), have transformed the treatment and prognosis of tuberculosis; but it must be admitted that in spite of the use of para-amino-salycylic acid (1949) and of more recent substances such as cycloserine, ethioniamide and kannamycin, tuberculosis remains in certain cases an eminently chronic disease that may end in death in a few years.*

# Psychological investigation

*Jacques A. GENDROT*

*Can one speak of a psychological investigation in medicine? Is a clinical examination of the state of mind of those suffering from organic diseases as important a diagnostic element as a radiograph or a biopsy? What place should be given to this method of investigation in the development of contemporary medicine? To what patients is this kind of investigation applied? What method of observation should be employed, and by whom should it be applied?*

This form of medical activity is so revolutionary that it amounts to a new conception of medicine. One might almost say that until the last few decades, the 'psyche' of man did not exist in medicine, which has reached the state of experimental sciences and exact techniques. But if biology was the science of the nineteenth century, psychology is the science of the twentieth: medicine, which stands at the cross-roads of these two powerful currents of research, is trying to synthesize them in the vast movement of thought called psychosomatic medicine.

For an increasing number of doctors organic disease is often no longer a simple physical affliction, but a crisis significant in someone's history; a crisis the interpretation of which depends on analysis of the personality regarded as a biological and psychological whole. For this kind of medicine there is no division into a substratum, the body, on the one hand, and a superstructure, the mind, on the other.

In this approach, the patient is a complete entity, body and soul, in all that he is, in his maturity as in his years of adolescence. From his lowest instincts to his highest spiritual conceptions, in success or in failure, in health or in sickness, he is, in anthropological medicine, an indissoluble whole. Consequently, the chief aim of psychological investigation in medicine is to reveal the psychosomatic correlations in the genesis and development of disease.

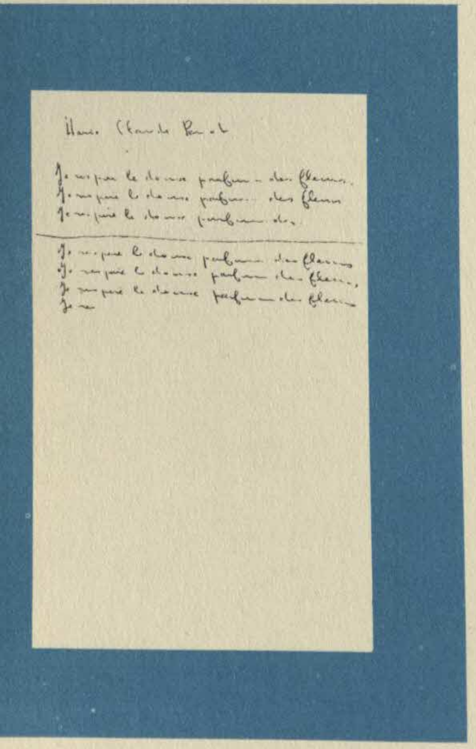


*Fig. 1. Graphology is one of the simplest techniques of psychological investigation: certain constants in handwriting betray certain psychological tendencies that are now well defined.*

It is known, for example, that the physiology of organs is co-ordinated by the higher nervous centres; but we forget that the cortical and sub-cortical centres, besides playing a part in somatic control, are centres for the integration of man's affective life. They are thus linked indissolubly with all emotional situations. The central regulation of physiological mechanisms in man is inseparable from this other central regulation, this remarkable capacity of the psyche to adapt itself to all situations, to preserve the equilibrium that is perpetually involved in the powerful and contradictory demands made by the instincts and by external reality.

The physiological principle of the stability of the internal environment (Claude Bernard) and the principle of constancy (homoeostasis) which governs the basal psychological equilibrium (Fechner-Freud) proceed from a common principle: namely, the fundamental unity of the human being, which expresses its identity and ensures its permanence throughout all its vicissitudes. The wisdom of the body and the wisdom of the soul are inherent and the disequilibrium of the structure must always affect the whole of it, even though clinical examination may disclose on the surface only an organic or a mental picture.

Thus the organs find themselves linked permanently with the psyche; that is to say, with the whole personality, with its developmental conflicts and its social problems; which, together, give to the person in good or bad health, his essential personality. Traditional medicine aims at establishing the type of disease that the patient exhibits; psychological investigation aims at explaining the peculiarity of the medical case in question.

There is unlimited scope for research. However, the totality of known facts may be grouped under certain main headings.

Clinical observation directed towards the *man* who is sick in body, and no longer merely towards the *organ*, soon reveals in an impressive number of patients the existence of a 'psychic factor' intimately linked to the history of the disease. Let us take the typical example of a sentimental disappointment accompanying the development of pulmonary tuberculosis, 'the malady of the melancholy passions' (Laennec). What the investigator is interested in is the whole morbid process, both psychic and somatic, expressing itself on the mental plane by a narcissistic injury[1] and on the physical plane by an organic disease. It is not a matter of separate studies of the affective reactions due to tuberculosis, any more than of sentimental disappointment considered from the point of view of a mental cause of organic illness. Psychosomatic observation must be concentrated on the total tuberculosis-personality of the patient, love-sick in that particular way, presenting a peculiar biological, or rather biopsychological, picture; that is to say, on his biopsychic condition, the outcome of which is an emotional failure coinciding with the development of tuberculosis, the personality and the organism being indissolubly associated in their total inadequacy to meet this combined assault. It is the concept of this morbid whole that constitutes the field of research.

The other spheres of interest spring from this basic idea: can organic symptoms be regarded as an expression of emotion or of psychological conflict? Are there psychological conflicts which are specific to the nature of certain organic diseases? Is there a psychosomatic personality, in the sense of a total disposition, physical and mental, for such and such an organic disease? And what is the origin, hereditary or acquired, of this psychobiological field?

Such, very briefly, are the ideas and aims of psychological investigation in medicine.

## Psychological tests and psychotherapeutic methods

The methods used for psychological investigation are far from being exhausted. Are there not as many psychologies as psychologists? Apart from empirical methods, which were the only methods until psychosomatic medicine began, we now have hypnosis, narco-analysis, and the psychological study of groups: among others, psychodrama and group psychoanalysis.

The methods most used in medicine are—in order of interest—the statistical method, psychological tests, and psychotherapy.

The interest of the standard questionnaire lies in its potential application to a virtually unlimited number of patients; for example, the whole population of a sanatorium, and statistical comparison with the answers given by an equal number of healthy persons; one can thus confirm an already known type of psychosomatic correlation (Fr. Pasche and P. C. Racamier).

The test method, ie, tests that reveal tendencies, not intellectual ability, has helped to make notable progress possible in the study of personality. Several tests are used together. From inventory tests psychological profiles may be constructed, these being based on a large number of questions that are intended to reveal the principal character traits (550 questions in the Minnesota Multiphasic Personality Inventory, or M.M.P.I.). Tests of projection[2] use images sufficiently suggestive, and yet ambiguous enough, to evoke significant data or possibly defence reactions from the different layers of the personality, the whole leading to a portrait of increasing accuracy; the Rorschach ink-blot test and the Murray test (figs. 2 and 4) are the best known. They make it possible to deduce from their results the probability of an organic process (the 'V' shape of the M.M.P.I. curve, detectors of psychosomatic troubles, the organic signs of Piotrowski, in the Rorschach test).

Handwriting, the study of which has always attracted a number of investigators (fig. 1) becomes a scientific test of the analysis of the personality (graphometry), free drawing of a tree in particular makes it possible to discover affective backwardness or regression (fig. 3). A large number of tests of projection are continually being studied.

The examiner must always take care to

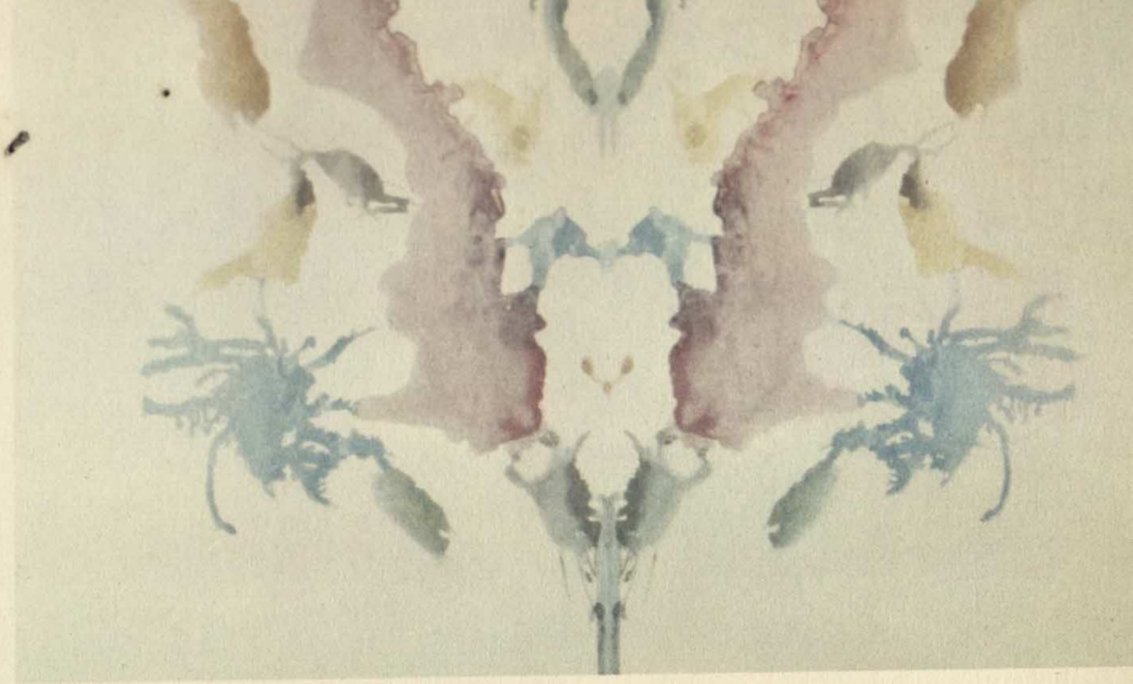


*Fig. 2. The Rorschach test (named after the psychiatrist who invented it) is based on a free interpretation of ink-blots made by a random mixture of different colours. The ambiguous and suggestive images that result are interpreted in different ways by different persons and this enables the psychologist to make a first sketch of the psychological profile. (Photo Lod: illustration supplied by the Centre Psycho-pédagogique, Paris).*

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(1) Narcissistic injury: *that which undermines the ideal image of the self.*

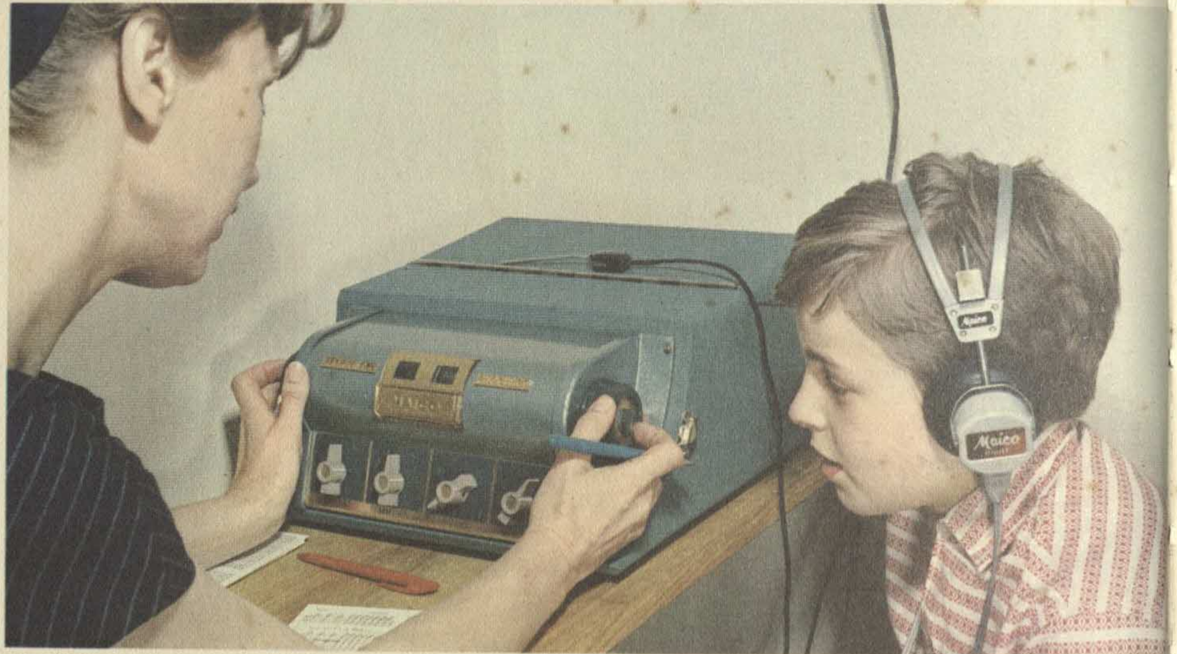
(2) Projection: *in psychoanalysis, the unconscious mechanism by which we attribute to other people, or to an object, our own basic tendencies.*

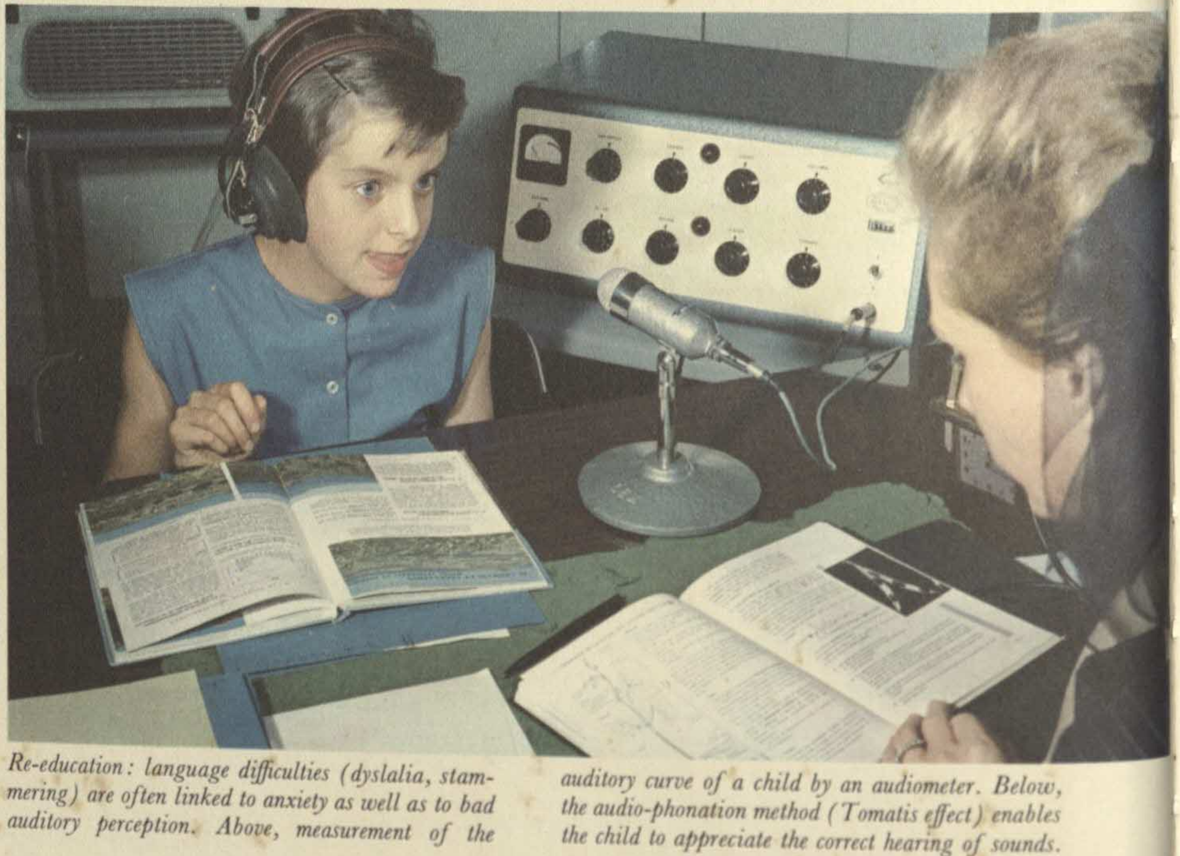
(3) Transference: *The shifting of all the patient's expectations, fears and hopes to the personality of the doctor. Corresponding to this transference from the patient to the doctor, there is, in the doctor himself,* counter-transference, *ie, all his reactions, conscious and unconscious, towards the patient, which he must elucidate and control increasingly in order that the patient's confidence and sincerity may not be impaired.*

# *Techniques of the psychotherapy of children*

*The development of the child is sometimes endangered by an unconscious conflict. The symptoms may relate to the body type (enuresis), or to character (anguish), or to the intellect (backwardness). The aims of the various methods of approach are to remove the inhibitions and to liberate the child's energy. (Photo Lod, taken at the Centre Psycho-pédagogique Étienne-Marcel, Paris.)*

*Psychotherapy: a child with inhibited affective development is liberating herself from her fantasies by means of a privileged relationship with the psychotherapist. Drawing or modelling enables her to talk about herself.*





*Re-education: language difficulties (dyslalia, stammering) are often linked to anxiety as well as to bad auditory perception. Above, measurement of the auditory curve of a child by an audiometer. Below, the audio-phonation method (Tomatis effect) enables the child to appreciate the correct hearing of sounds.*

*Symbolic play: modelling and painting are means of expression by which the child can project his interior world: he models, constructs, and chooses and mixes colours to his liking.*

keep himself in the background, behind the objective instruments of the test, but the valid interpretation of the responses requires a high degree of intuition and a clinical sense developed by long experience. Nevertheless, the best psychological examination, based on the most extensive cross-checking of superimposed tests, cannot dispense with clinical examination, of which it is a valuable, though necessarily partial, informative element. The clinical method of psychotherapeutic examination is incomparably the most fruitful; all recent discoveries of importance in psychosomatic medicine have originated in this.

In the clinical method the basis of investigation is the relationship between the doctor and the patient. This relationship is established by means of transference,[3] which is the key to the whole experiment. It is in the human resources of such a contact that the patient finds the additional energy which enables him to grapple with pathogenic conflicts. The investigation is also a therapeutic procedure; the patient only confides his problems to the doctor because he hopes that a new solution of his troubles will ensue.

## *The usefulness of psychoanalysis*

It is well known that this method of investigating the psyche—devised by Sigmund Freud—has achieved its full scope in psychoanalysis, the method of elucidating psychological processes, especially unconscious ones. All modern psychotherapy is derived from psychoanalytic theory and practice.

This method, which is both exploratory and therapeutic, demonstrates the reality of psychosomatic correlations and the scientific control of these correlations is shown by changes in the physical condition. For example, if an asthmatic condition disappears during the exploratory interview and is replaced by an emotional crisis showing itself in sorrow and anger, these are grounds for saying that the asthma was an expression of these repressed emotions; or when a deep psychological investigation of a tuberculous patient, who has been resistant to antibiotics for months, reveals that in fact he wants to die, and when the investigation of his problem has been taken in hand and has opened up for him a new perspective of existence, a reversal of the biological reactions sets in (the antibiotics again playing their curative part), one has grounds for saying that the psychological resignation of the patient was accompanied by a collapse of his biological defences.

These, of course, are simplified examples; psychological investigation, as has been shown, does not confine itself only to psychosomatic correlations between the actual psychical condition and the co-existant organic state. It seeks to go back into the case history of the individual and to trace the origin of the conflict between the moral and the organic personality, where the trouble lies, so that steps may be taken to remedy it.

The problem which then presents itself is that of adequate preparation for employing the best method to use, and, connected with this, of deciding who are the people best qualified to undertake this type of investigation. The answer is clear: it is from a harmonious two-man team—a physician who really understands psychosomatic correlations, and a psychotherapist experienced in psychoanalysis and the treatment of psychic troubles, that investigation will be most fruitful, because it will be the best equipped. Only a physician will have the necessary authority to make psychological investigation acceptable. In addition, he is the patient's guarantee that his organic defences (and the treatment they require) will be respected as far as is necessary. More often than not, only the psychotherapist, well acquainted with the secrets of the conscious and unconscious dynamics of psychic life, will know the best way to approach them and how to bear to the end with the patient's psychological reactions and conflicts without affective and untimely interference. The results of psychosomatic investigation thus practised will be discussed by the two practitioners according to their plan.

The technique of psychological investigation has been best defined by F. Deutsch as '*associative anamnesis*'.[4] This is the ideal technical attitude for revealing what is hidden, the psychical conflicts and the psychosomatic

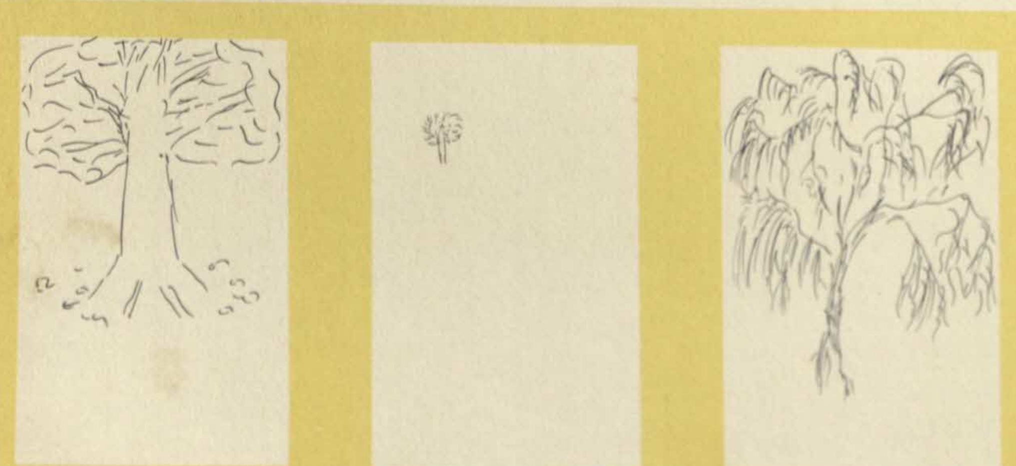


*Fig. 3. The 'tree' projection test invented by Koch. The three free drawings of the tree indicate: one, a voracious appetite; two, a marked effacement of the self; three, a poetic but evanescent relationship with reality.*

(4) Anamnesis: *the history of the illness supplied by the patient himself, or more precisely, a case history of the psychosomatic correlations.*

(5) Pathogeny: *the study of pathological mechanisms.*

(6) Aetiology: *the study of the causes of disease.*

(7) Nosology: *the classification of diseases.*

(8) Functional disorder: *without organic damage, but with a constant anxiety component. Spasms, certain forms of nausea and vertigo, various aches and pains and other forms of malfunction are of this type.*

correlations. In the course of examination, which proceeds without direction by the therapist, the patient is left to reveal his history spontaneously. It is he who, in his own time and according to his own more or less active resistance to the revelation of his own affective personality, reveals all the elements that need to be observed. He will oscillate spontaneously between the plane of his physical symptoms and that of his psychological conflicts, thus revealing—by uncovering it—the psychosomatic unity of his illness. (Marty and Fain, de M'Uzan). The therapist's role consists in setting the normal series of associations in motion again and, by obtaining from them the appropriate result, in allowing the patient to express himself completely without reserve.

## *What are the results?*

There is not room here to study the theoretical and practical results of this new method of medical investigation, but only to summarize their principal aspects. Theoretically speaking, far from reviving the sterile dispute about the relation between the physical and the moral sides of personality, psychosomatic medicine—the daughter of psychoanalysis—has the great merit of studying man in his totality. The old dualism of mind and body, bogged down in the purely abstract conceptions of classical psychology and in the purely concrete conceptions of morbid anatomy and pathology, disappears at the level of the biological unconscious; that is to say, at the level of the dynamism of the instincts in the sense of an undifferentiated biopsychical substrate. Interrelations at a deep level between the psychical unconscious and the vital functions give rise to correlations between disease and character (Ch. Brisset). The concepts of disease and of cure must be completely recast. All the pathogeny[5] and aetiology[6] of disease must be thought out again. The importance now attached to psychological conflicts and traumas in early life, especially the affective deficiencies of early infancy (Spitz), as well as the feeble ego (affective immaturity, regressions, neuroses), which result from these, has profoundly reshuffled fixed ideas about heredity and the constitution.

The integration of the idea of anxiety, almost ignored in the practice of traditional medicine, overthrows the purely physico-chemical conception of organic medicine: thus the patient's mental and emotional situation is no less significant than his infection by micro-organisms. In the same way, in chronic diseases, the conflict between dependence and aggressiveness determines the origin and prognosis of the disease to the same extent as do the cellular defences. Whether they are organic or psychological, the reactions of the individual are linked to his history, to his harmonious development or to his ancestors. The totality of these correlations constitutes a new nosology,[7] which is still inarticulate; examples of it are psychosomatic profiles (Fl. Dunbar) and emotional pathogenesis (F. Alexander).

So far as practice is concerned, this humanizing of medical technique does not necessarily complicate the doctor's task; on the contrary, it quite often simplifies it and increases its efficiency by eliminating useless examinations and injurious treatments. The therapeutic possibilities of this type of investigation cannot yet be precisely defined. First, the resistance of doctors must be overcome, so that it may become possible by the fruitful collaboration of research workers in all fields to reach its legitimate boundaries.

For these reasons one must be cautious of certain psychosomatic theories, which recommend a systematic psychological investigation of all patients suffering from organic disease, or of certain ambitious hypotheses, such as those of C. Kent, who postulates the existence in man of 'hidden vital and psychological resources' and suggests that investigations taken as far back as the prenatal stage would activate these hidden resources.

## *The future*

Psychological investigation in medicine is now called for in three kinds of disease; in *functional disorders*[8], which account for almost one third of the doctor's daily consultations; in purely *psychosomatic diseases,*[9] the number of which is limited, but may be increased by actual investigations (gastro-duodenal ulcers, arterial hypertension, numerous allergic manifestations, etc.); and in all cases (medical or surgical) that *interfere with the personality;* that is to say, in every affection, acute or chronic, which—although it may have its own etiological, clinical, and therapeutic identity—becomes so involved with psychological disturbances in the patient that all the psychosomatic defences against the organic process are modified; in other words, to such an extent that the prognosis of the disease is altered.

To sum up, by restoring medicine to its true human dimension, psychological investigation is on the way towards bringing to the science of prognosis the basis that Hippocrates wished it to have.

(9) Psychosomatic diseases *are characterized by an initial functional, reversible phase; an irreversible phase with a lesion; the possible transition of one psychosomatic disease into another; evidence of psychosomatic correlations. (B. C. Meyer.)*

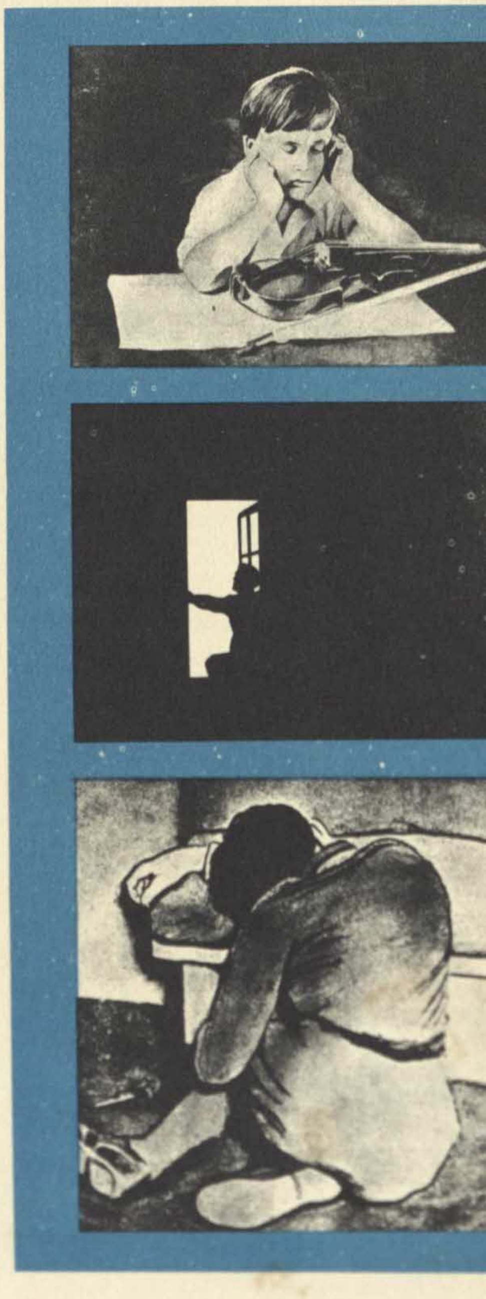
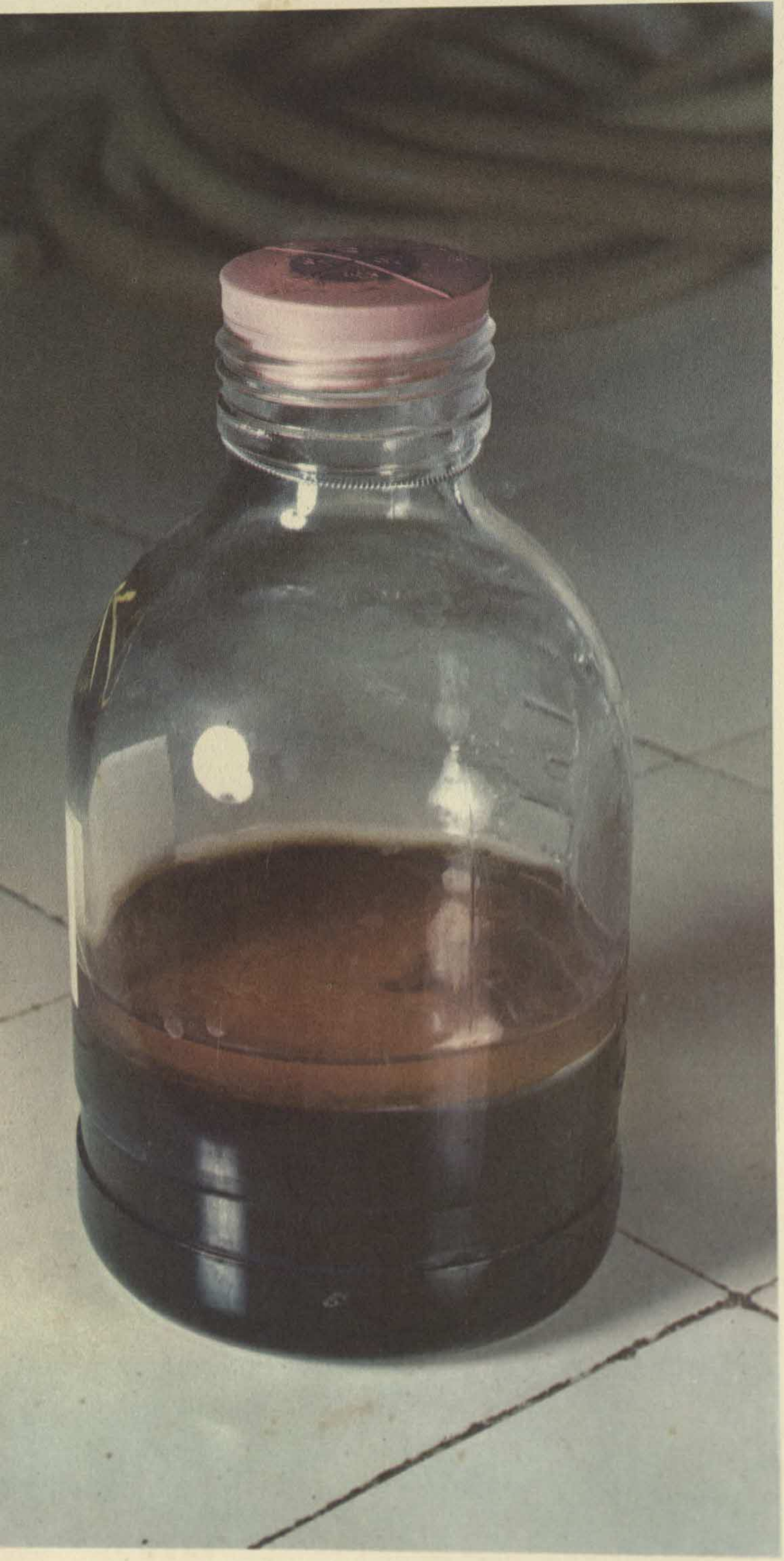
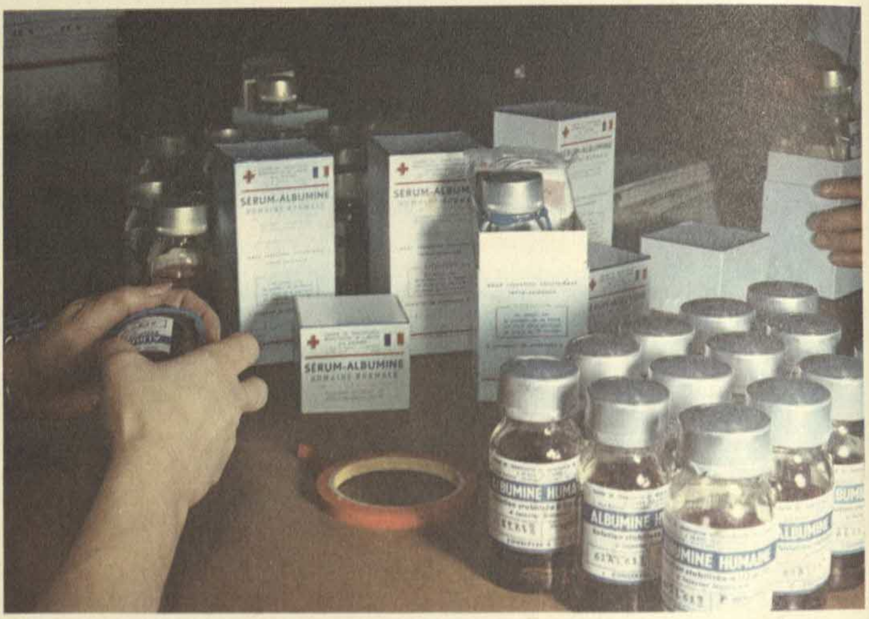


*Fig. 4. Another projection test: three illustrations of Murray's thematic apperception test. The interpretation of these three illustrations throws a light on the affective state of the patient and on his personality.*

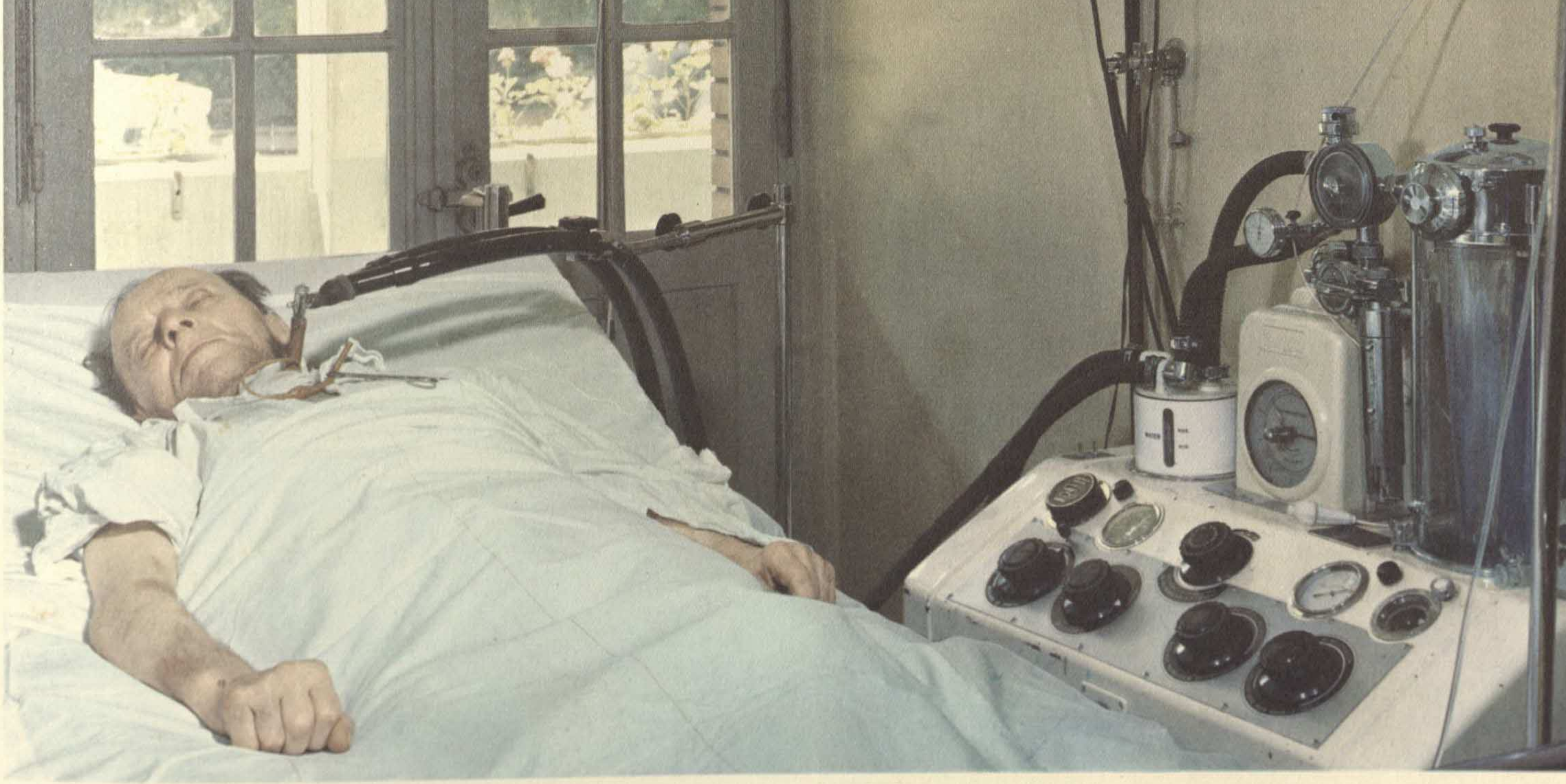
# PART TWO





*However difficult it may be, the diagnosis of disease is only one of the problems which the doctor must solve to his own satisfaction before he takes the next step. From then on, he must considerably enlarge the sphere of his investigation, by carefully assessing the reactions caused by the disease in the patient's body and personality. The existence of a lesion or of a striking deterioration of one function may result in others,*

# *Controls and adjustments*



*affecting organs widely separated, but whose functions are reciprocally controlled. In every case, the doctor must therefore proceed to make tests of the humoural and nervous functions of the organism. Blood analysis (illustrated on the left-hand page) is one of the most important of these. Other techniques, besides the usual form of treatment, make it possible to regulate the patient's functions, or, as we say nowadays, to recondition him. Anaesthesia, artificial hibernation, and especially resuscitation (illustrated on the right) are the most important of these methods.*

*(Photos Lod; those on the left taken at the Jean Julliard Centre de Transfusions Sanguine de l'Armée; on the right, at the Hôpital St. Antoine, Paris, by courtesy of Professor Kourilsky).*

# Control of the fluid balance

## *Jean-Pierre SOULIER*

*Claude Bernard has said that the constancy of the internal environment is the guarantee of a free and independent life. It ensures the nutrition of the cells and the elimination of waste products, whatever the physiological conditions may be. Knowledge of the exchanges between the body fluids and the cells is indispensable to the maintenance or re-establishment of this constancy when it is affected by pathological disturbance. Dr Jean-Pierre Soulier here explains the methods of control and treatment for the re-establishment of constancy of the internal environment.*

All adverse conditions (surgical operation, accident, intoxication, acute infectious disease) endanger the internal equilibrium. This equilibrium or 'homoeostasis', mainly concerns the circulation, oxygenation, and electrolytic balance of the tissues and body fluids. When it is jeopardized, by whatever cause, certain compensating mechanisms—always the same ones—come into action.

A new procedure, known as 'resuscitation', aims at restoration of this equilibrium. Resuscitation is concerned not with the cause but with the effects of non-specific disturbances. Originally limited to the treatment of 'post-operative illness' (a term suggested by Gosset for disturbances caused by surgical operation), resuscitation has been extended to include what Hamburger has called 'medical resuscitation'. This consists of a symptomatic treatment which aims at re-establishing the organism's equilibrium and gaining time in which to give curative treatment, which attacks the cause, a chance to act effectively.(1)

This complex undertaking requires many controlled tests; the doctor, taking the place of the regulatory mechanisms of the organism, needs a laboratory that operates for twenty-four hours a day. Such care can be provided only in certain specialized departments of hospitals. One method, however, which is essential to resuscitation, namely, transfusion, can be very simply used anywhere and under any circumstances.

## *Hydro-electric equilibrium*

Fifty to seventy per cent of the body weight, according to age and obesity, is represented by water. Hydro-electric equilibrium is maintained by a very delicate balance between the entry of water in various ways (in food and drink) and its elimination (perspiration, water in the urine and faeces).

This water is distributed in the organism both inside and outside the cells, 5 per cent of it being contained in the blood circulation. The extracellular water which bathes the cells represents about 20 per cent of the body weight, but it is of fundamental importance: it constitutes the 'internal environment' spoken of by Claude Bernard.

Increase of the extracellular water (hyperhydration) shows itself by the appearance of oedemas,(2) which are at first apparent only in an increase of weight. This retention of water is caused by electrolytes, of which sodium ions (figs. 1 and 2) play the preponderating role.

Dehydration shows itself by a simultaneous loss of water and salts and a reduction in sodium content: the skin is dry, blood pressure is low, and there is considerable physical weakness. The blood is concentrated and the urea level is usually increased.

Changes in the water content of the cells themselves occur only if the extracellular hydro-electrolytic equilibrium is disturbed: cellular dehydration is shown by thirst,

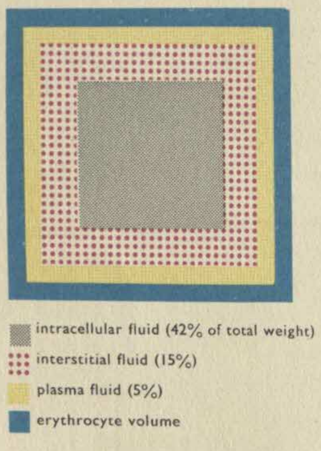

▨ intracellular fluid (42% of total weight)
⁙ interstitial fluid (15%)
▨ plasma fluid (5%)
■ erythrocyte volume

*Fig. 1. Distribution of water in the various parts of the organism, showing the extracellular water, linked to the proteins of living matter, and the water of the interstitial fluids and of the blood plasma.*

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(1) *In certain fields resuscitation is able to provide complete or at least temporary vicarious artificial restoration of failing functions.*

(2) Oedema: *infiltration of the various tissues, especially the connective tissue of the skin or mucous membranes. For details, see the chapter on coagulation of the blood by J.-P. Soulier (Vol. 5. p. 35).*

(3) *In this regulatory mechanism the lung plays an essential part in eliminating the carbon dioxide which results from bicarbonate displacement. The kidney plays a no less important part by eliminating organic acids, either in their natural form or as salts of ammonia. Gaseous or fixed alkaloses and acidoses are distinguished according to their mechanisms.*

somnolence, respiratory disturbances, and fever. The opposite of cellular hyperhydration reveals itself in digestive and nervous disturbances.

The acid-base equilibrium is jealously preserved by the organism: its failure has grave consequences. The plasma contains buffer systems, the most important of which is that of the bicarbonates, which represent the 'alkali reserve' of the organism.[3]

Among the ions that are of importance in resuscitation, potassium has a special importance. Potassium deficiencies and, above all, excess of potassium have a serious effect on the heart. When the potassium rises above 8 milliequivalents per litre, sudden death may occur.

## *Excretory and respiratory equilibrium*

The kidney, together with the brain, is the organ which suffers most from disturbances of circulation. It plays a considerable part in the organism; its task is to eliminate the waste products of nitrogen metabolism and to govern the metabolism of water and electrolytes. Any kidney disturbance is shown by a rise of the urea level in the blood.

All renal insufficiency shows itself by excess of nitrogen, hydro-electrolytic disturbances, haematological disorders, and repercussions on the cardiovascular system. At their worst, these disturbances result in complete failure to produce urine. Treatment consists in extra-renal cleansing by blood dialysis in an artificial kidney and in very strict dieting (restriction of water and nitrogenous substances).

The function of respiration is to carry oxygen to the cells and to eliminate carbon dioxide. Gaseous exchanges between pulmonary alveolus and capillary blood are effected by diffusion. Most carbon dioxide is carried in the blood in the combined form of bicarbonates, but the fraction of it that is directly exchangeable is the small fraction that is dissolved in the blood (one-twentieth of the total carbon dioxide in the plasma).

Oxygen in the blood is combined with haemoglobin, which plays the chief part as carrier and reservoir of oxygen; but in this also it is the small fraction dissolved in the blood that takes part directly in the exchanges in the lung or in the tissues.

Serious disturbances of the respiratory function result in death through anoxia (failure of the oxygenation of the tissues) or through retention of carbon dioxide (hypercapnia). Usually, the two mechanisms are combined. Respiratory embarrassment, cyanosis, circulatory troubles, and nervous symptoms are the expression of disturbances of gaseous exchanges.

Urgent treatment involves the administration of oxygen, and, if necessary, clearing of the respiratory passages (laryngeal aspiration, intubation, tracheotomy). Artificial respiration or respiratory aids are applied to patients who, as a result of affections of the respiratory centres or muscle paralysis, cannot adequately ventilate their lungs.

## *Cardiovascular equilibrium*

Resuscitation seeks, above all, to re-establish a cardiovascular equilibrium compatible with life. A fall in blood pressure and a decrease in the blood supply accompany every kind of acute cardiac insufficiency and every severe reduction of the mass of circulating blood.

Among acute cardiac insufficiencies requiring urgent resuscitation are:

1. The *acute conditions of heart and lungs* complicating pulmonary embolisms, certain asthmatic states, and certain types of pneumothorax. Insufficiency of the pulmonary circulation aggravates respiratory insufficiency. Thus a vicious circle is established and it is important to break this. The electrocardiogram will show a characteristic tracing.

2. *Paroxysmal left ventricular insufficiency with acute oedema of the lung* may be seen in cases of hypertension or in patients with an over-loaded circulation. The picture is that of acute asphyxia, for which the patient must be copiously bled; injections of sedatives and cardiac tonics are also necessary.

States of shock and vascular collapse must be distinguished from sudden heart failure. In these states it is not that the cardiac pump is inadequate, but that the content of the blood vessels is severely reduced, so that the heart is working almost empty.

Haemorrhage is the chief cause of collapse and shock. This is the essential factor in shock resulting from surgical operations or from injuries. But the reduction of the mass of the blood can also affect only the plasma portion of the blood. It is this that is seen in shock due to burns or crushing, in which, as a result of the selective loss of plasma, the blood becomes concentrated (fig. 3).

Shock, at first compensated for by a whole series of defences of the organism (contraction of the spleen and the small vessels and the

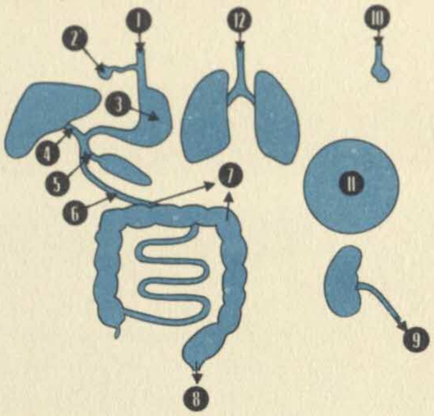

*Fig. 2. Entry and exit routes of fluid in the human organism: 1. alimentary water; 2. saliva (1,500 cc); 3. gastric juice (2,200 cc); 4. bile (700 cc); 5. pancreatic juice (700 cc); 6. intestinal juices (3,000 cc); 7. total reabsorbed water (10,000 cc); 8. faeces (100 cc); 9. urine (1,400 cc); 10. sweat; 11. endogenous formation of water (300 cc); 12. cutaneous and pulmonary perspiration (800 cc).*

*([4]) The liquid plasma in which these constituents are bathed contains proteins as well as salts and sugar; albumin, which represents 60 per cent of the plasma proteins, is responsible for the osmotic pressure of the plasma. The globulins are classified according to their speed of migration in an electric field into alpha-globulins (represented especially by haptoglobin), beta globulins (lipoproteins), and fibrinogen and gamma-globulins (antibodies). The plasma contains numerous factors concerned in coagulation. Prothrombin is changed into thrombin under the influence of an endogenous or exogenous thromboplastin in the presence of ionized calcium. Thrombin transforms fibrinogen into fibrin (or coagulum).*

*([5]) Blood transfusion requires that the doctor has a thorough knowledge of blood groups, not only of the four major groups, A, B, AB and O, but also of the Rhesus factor (85 per cent of individuals are Rh-positive) and of the sub-groups of the*

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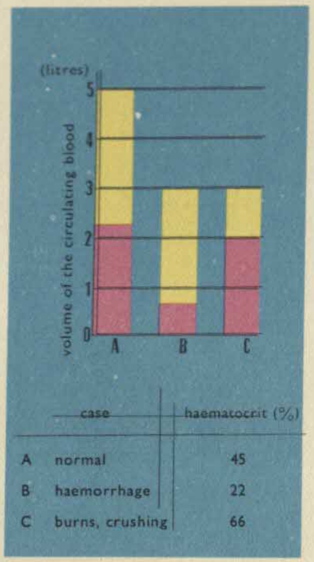


| case | | haematocrit (%) |
|---|---|---|
| A | normal | 45 |
| B | haemorrhage | 22 |
| C | burns, crushing | 66 |

*Fig. 3. Modification of the haematocrit in haemorrhages and traumas.*

continued from previous page

*Rh-system. Other groups, though seldom likely to cause blood incompatibilities, must be taken into account in diseases requiring several transfusions (Kell, Lewis and S groups, sub-groups $A_1$, $A_2$, etc.). Hence the importance of a thorough knowledge of the acts of blood compatibility.*

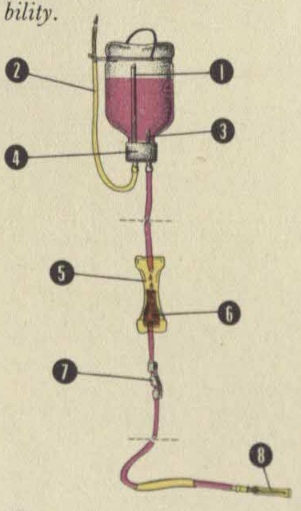


*Fig. 4. An apparatus containing plasma ready to be injected into a vein. 1. tube; 2. intake of sterile air; 3. needle with three holes; 4. stopper; 5. transparent filter chamber; 6. filter for intercepting micro-clots; 7. clamp; 8. injection needle.*

exclusion of certain vascular areas) soon becomes irreversible if the mass of circulating blood is not restored by abundant transfusions. In this condition, the use of vasconstrictors (noradrenaline, phenyephrine) may still save life, provided that transfusion has preceded, or is at any rate accompanied by, the administration of pressor drugs, which act on blood pressure.

## Syncope and cardiac arrest

*Syncope* is only a transitory arrest of the heart, due, in general, to excitation of the vagus (pneumogastric) nerve. It usually disappears if the patient lies down with the head low and the limbs raised.

If necessary, one can inject 0·5 mg of atropine sulphate. In exceptional cases, involving defective innervation, one may have to inject ephedrine or procaine.

Complete *cardiac arrest* results in death in a few minutes. It is possible to resuscitate a patient with an arrested heart by injecting the heart with traces of adrenalin or with calcium chloride, but it is necessary as a rule to apply external cardiac massage and artificial respiration; if necessary, an emergency thoracotomy must be performed, so that direct massage can be given. This is one of the most dramatic resuscitation procedures, which in the absence of hypothermia techniques, must be carried out within a few minutes of the patient's collapse. The heart can still start again between the sixth or the eighth minute and the thirtieth minute, but if intracheal oxygenation under pressure through a tube has not been begun immediately, life may be preserved, but not immunity from damage to the brain. Lesions in the nervous system caused by anoxia establish themselves very rapidly and are irremediable.

## Control of blood equilibrium

Red blood cells (erythrocytes) carry oxygen from the lungs to the tissues; white blood cells (leucocytes) fight against infection, some, derived from the bone marrow (polymorphonuclear), by their phagocytic activity, others (plasmocytes, lymphocytes) by producing antibodies. Blood platelets (thrombocytes) play an essential part in the mechanism of haemostasis.[4]

In certain diseases the equilibrium of the constituents of the blood and of the proteins is upset, as, for example, in acute haemolysis attended by destruction of red blood cells, and in haemorrhages resulting in a severe reduction of the mass of the blood in the organism, while thrombosis can result from intravascular clotting.

The control of equilibrium in the blood, like that of cardiovascular balance, will, when reduction of the mass of the blood occurs, necessitate blood transfusion, which is one of the principal weapons of resuscitation.

Transfusion[5] of the whole of the blood makes it possible to supply the elements necessary for the transport of oxygen, for defence against infection, and for the formation of a 'platelet plug' (white thrombus). It enables the mass of the circulating blood to be re-established and states of shock or vascular collapse to be overcome. Not the least of its advantages is that it supplies the coagulating factors that are required for haemostasis.

Nowadays, transfusion is indirect and involves the use of blood in bottles containing ACD solution (acid, citrate, and dextrose). The blood can be preserved in a refrigerator at +4° for two to three weeks (fig. 4).

## Derivatives of the blood

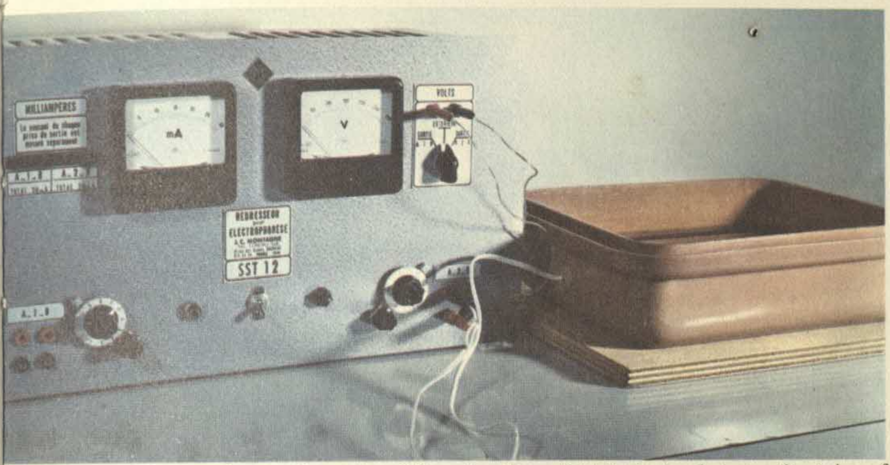
Although a complete transfusion of blood serves perfectly for treatment of traumatic or post-operative shock and of a haemorrhage, it may be preferable to inject only the blood fraction which the organism needs: ***concentrated red cells***, in states of acute anaemia in sufferers from cardiac and renal troubles, in which a sudden increase in the mass of the blood is to be feared; ***plasma*** or the ***albumin*** of plasma (V fraction of Cohn's fractionation) in patients with blood concentration (due to burns or crushing); ***fibrinogen*** (fraction I of Cohn) and other clotting fractions (antihaemophilic fraction A or B, and factors in the prothrombic complex) for the treatment of acute haemorrhagic syndromes.

When blood or its derivatives are not available, ***plasma substitutes*** can be used. These are colloidal solutions (polyvinyl-pyrrolidone, dextran, and modified gelatine) which stay in the blood for from twelve to twenty-four hours. But these substitutes cannot replace either the administration of red cells or that of the factors needed for coagulation.

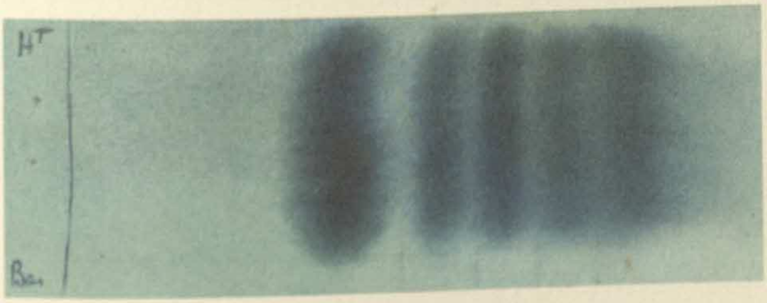
To sum up, resuscitation seeks to re-establish the constant conditions of the organism. The battle with asphyxia, as well as the correction of fluid and cardiovascular disorders, makes it possible in many cases to save lives which a few years ago would have been lost. Blood transfusion is one of the most important weapons in the resuscitator's armoury.

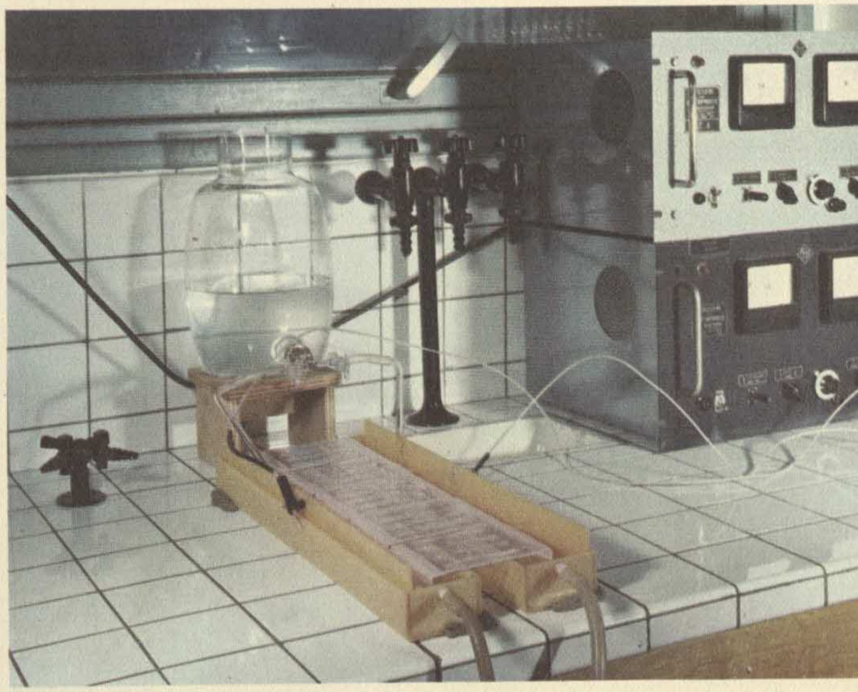
# *Electrophoresis*

*This is a method of identification and testing which makes it possible to separate the various blood proteins that carry different electric charges and move at different speeds under the influence of an electric field.*

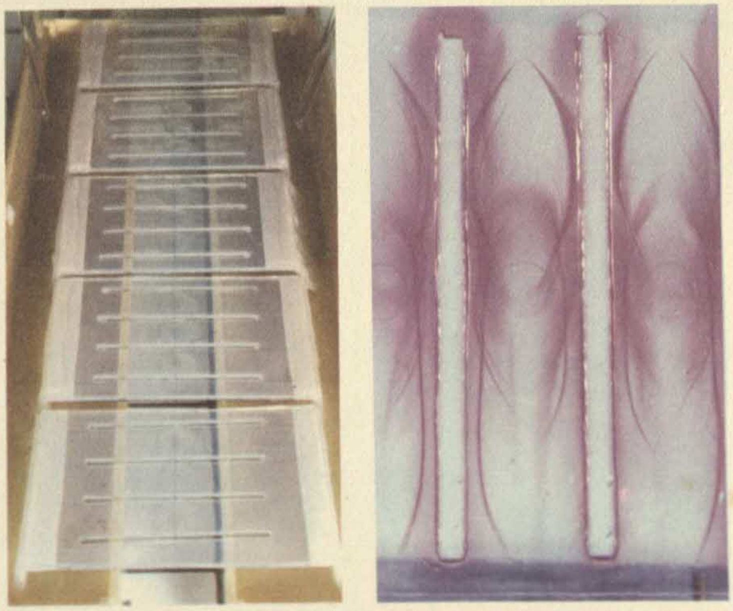


Paper electrophoresis: *The migration of biological substances (proteins of human serum) is here shown on a band of filter paper. From above downwards: (1) the voltage rectifier-stabilizer; (2) trays containing the buffer solution, which keeps the pH constant; (3) the placing of serum on bands of filter paper with a micropipette; (4) the picture given by electrophoresis.*





*Immuno-electrophoretic analysis on an agar plate. Above: a voltage-rectifier stabilizer with, on the left, the trays and apparatus for circulating the buffer solution (the agar plates are already in the trays ready for electrophoresis).*



*Left: detail of the agar plates before immuno-electrophoresis; right, the result: normal serum in the centre, pathological sera on its left and right.*

# Control of nervous activity

*Michel BOISVERT*

*Deliberate control of nervous activity has given rise to a new science, anaesthesiology, the rapid development of which is due to the discovery of new chemical substances, or of new methods which can temporarily abolish consciousness and pain. Thanks to these methods, prolonged and even dangerous surgical operations can be carried out successfully.*

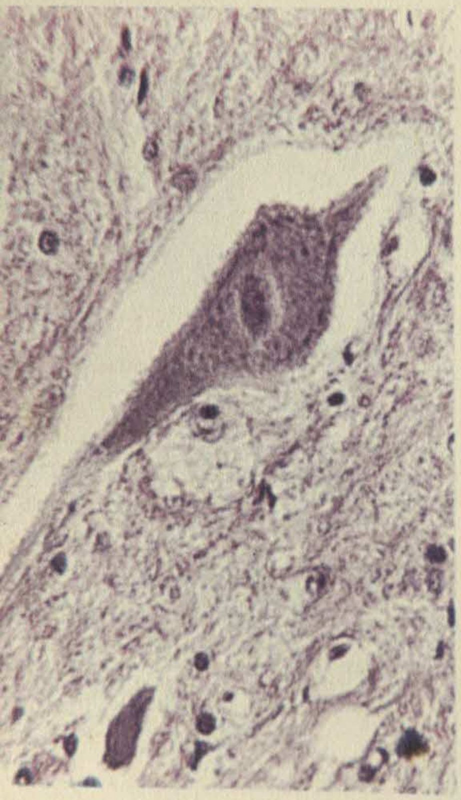


*Fig. 1. Nissl bodies are characteristic structures in the cytoplasm of nerve cells. (Photo Lod).*

The day is perhaps not far distant when we shall have drugs capable of controlling the mind itself. Already a new product, tricyano-amino-propane (TAP) has been announced which makes possible a considerable increase in an individual's suggestibility. Collective chemical hypnosis, that dream of totalitarian states and triumph of great propaganda machines, is perhaps at our gates.

These anticipations of Aldous Huxley's *Brave New World* thrust themselves on the mind when one thinks of the formidable therapeutic arsenal that the doctor has for controlling nervous activity. This activity assumes many forms that are both conscious and unconscious, chemical and electrical, and incredibly complex. The electrical activity of the central nervous system can be recorded through electrodes placed on the cortex or the scalp which produce a tracing (the electroencephalogram) showing rhythmic oscillations by which one can read spontaneous cerebral activities as well as activities produced by drugs that act on the nervous system.

## Depressants and stimulants

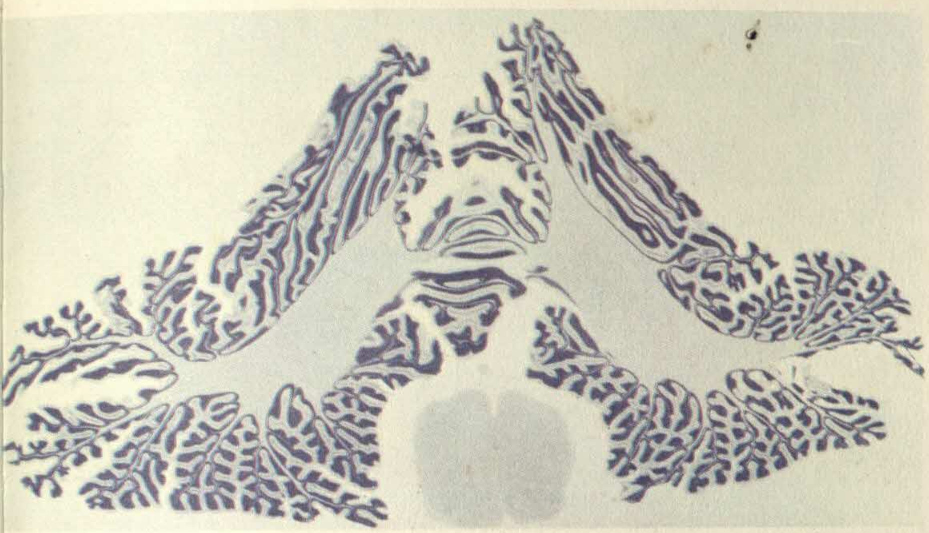
These drugs are usually grouped under two headings: *depressants* and *stimulants*. The depressants are subdivided into a great variety of categories. First, there are the general anaesthetics. Anaesthesia means, literally, absence of sensation. General anaesthesia implies the disappearance, not only of all feeling, but also of all consciousness.

The narcotics constitute a second group of depressants of the central nervous system. Narcosis is a state of analgesia (absence of pain) accompanied by stupor. Narcosis differs from anaesthesia in that the pain disappears before sleep and unconsciousness supervene, if in fact they do supervene. The narcotics most used are morphine, pethidine, codeine, etc.

Hypnotics (sleep-inducing drugs) form a third group, to which may be added sedatives that engender calm and tranquillity (diminution of cerebral excitability) without, however, producing sleep; among this type are the barbiturates (pentothal, amytal, phenobarbitone) chloral and the bromides. A fourth subdivision includes the analgesics, which dull the sensation of pain, without, however, causing stupor or unconsciousness; eg, the salicylates and aminopyrine. The anti-epileptics and the central relaxants of the skeletal muscles also constitute well-differentiated classes.

Finally, there are the now famous ataraxics or tranquillizers, generators of 'peace of mind'. These drugs have revolutionized the field of mental diseases, from neurosis to psychosis. They are broadly grouped into two large families: those which include the derivatives of phenothiazine (largactil, sparine, pacatal, nozinan, etc) and those which include the Rauwolfia alkaloids. Their chief effect is to relieve anxiety, but their effects on the nervous system are various: they are used with success against nausea, vomiting, itching, hyperpyrexia, asthma, allergic reactions, hypertension and *stress* of all kinds.

These drugs affect the nervous system at different levels. Compounds which have individual and specific activity are rare: the doctor who is asked to control a disorder of the nervous system must often prescribe a drug which, besides having the desired effect, will also produce an undesirable depression of some other perfectly healthy cerebral function. There is no doubt that the pharmacopoeia will be soon



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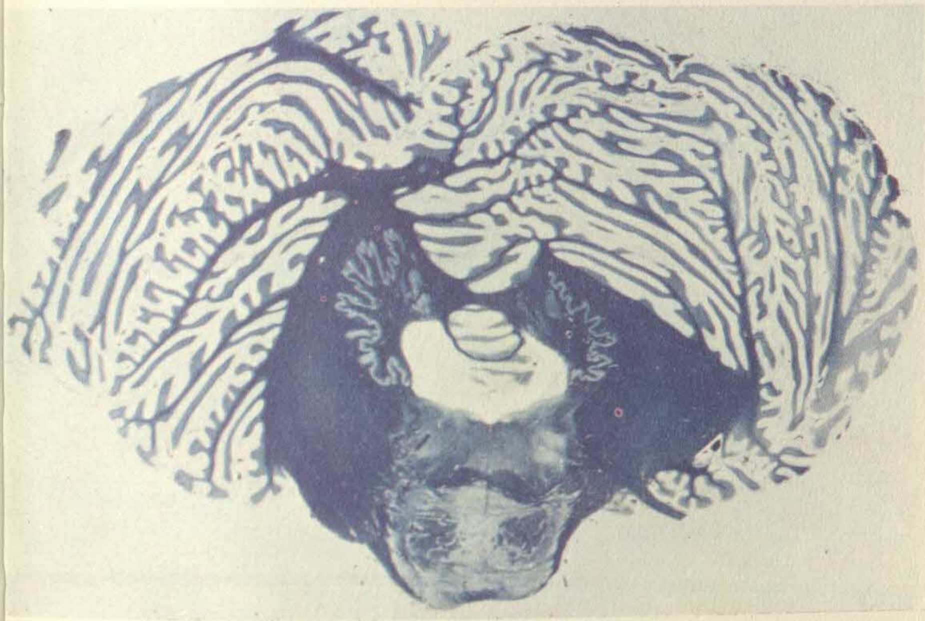

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*1 and 2, section through the cerebellum after impregnation with silver salts. 3, microscopical section through the granular layer of the cerebellum; Purkinje cells at the bottom of the photograph. 4, microscopical section through a sympathetic nerve ganglion (Masson's trichromatic stain with aniline blue).*

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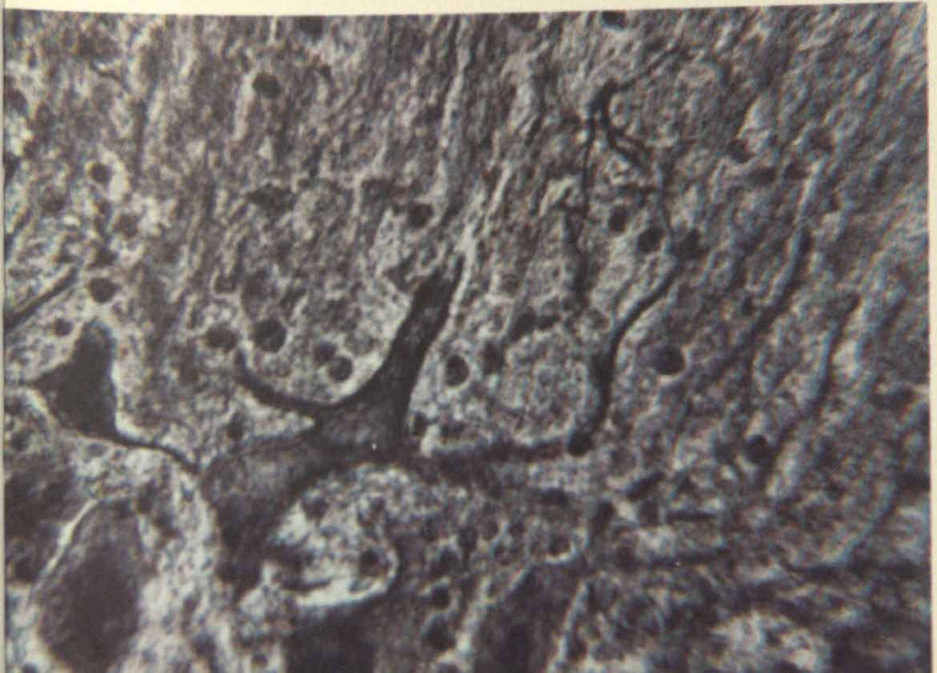

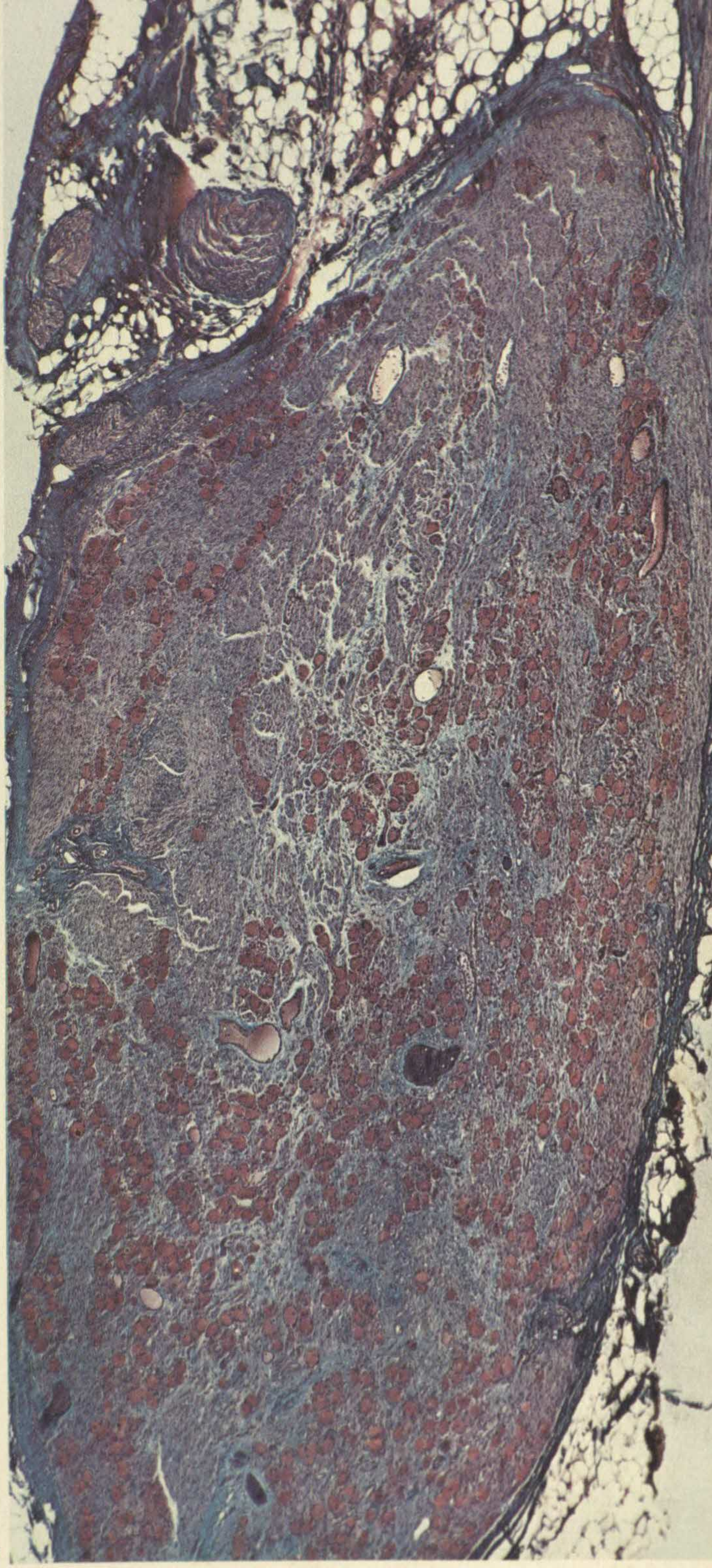

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*Fig. 2. In order to control the activity of the nervous system, it is necessary to act on certain visceral centres in the brain.*

enriched with substances the action of which is just as powerful, but more circumscribed.

The *stimulants* of the central nervous system form a less important group than the depressants. It has been established, in fact, that where stimulants are used they involve an equally intense and long-lasting depression. For this reason continued stimulation soon becomes dangerous. The value of such substances as coramine, picrotoxin, amphetamine, camphor, strychnine, ritalin or vandid (Emivan) is chiefly limited to emergency treatment: for example, in central depression due to barbiturate addiction, various kinds of poisoning, respiratory depression, etc.

The autonomic nervous system, sympathetic and parasympathetic, also has its pharmacopoeia, which is infinitely complex. It must be remembered that there is no organic disturbance—whether it involves cardiac rhythm, blood pressure, the tone of the arteries, the state of contraction of the digestive tract, lung ventilation, the salivary, gastric, or sweat secretions—that cannot be corrected either by stimulation or by selective blocking of the elements of the autonomic nervous system.

Thus, although the nervous system is far from having yielded all its secrets, the biological sciences have nevertheless succeeded in revealing several of them and in partially mastering the functioning of the system, as well as in bringing into the scientific orbit a field in which empiricism formerly held sway.

## General anaesthesia

The suppression of pain—especially pain connected with surgery—is one of the oldest dreams of humanity. It fell to young America to fulfil this dream, for between 1842 and 1846 Long, Wells and Morton succeeded in producing unconsciousness and insensibility during surgical operations. The triumph of this technique was achieved on October 16, 1846, in the surgical theatre of the Massachusetts General Hospital, when the surgeon John Warren removed a submaxillary tumour from a patient (Gilbert Abbott) whom he had made completely unconscious and insensible by the inhalation of ether. News of this discovery soon travelled all round the world. From that time onwards hospitals ceased to echo with the agonized cries of patients bound down on to a table and whose tortures were shortened only by the incredible speed with which surgeons operated in those days. Hardly a century separates us from those scenes of horror, yet we have since travelled far. In 1965, we are far removed from the chloroform compress, formerly held in place by the nurse or orderly. The anaesthetist is now a medical specialist. During the operation he controls a complex scientific arsenal of gases and liquids. As a physiologist and a resuscitator, he can use injections and transfusions to correct disturbances caused in the patient by the operation. Devices connected to the patient—the 'monitors'—report to the anaesthetist all the time on the activities of the heart and brain and the state of oxygenation; analyses of the blood keep him informed of the advent of possible disturbances in equilibrium.

This refinement of the techniques of anaesthesia has altered the older practices of surgery: the surgeon no longer operates by the clock; the acrobatic feats and the spectacular 'performances' of the masters of yesterday have given place to a type of surgery that is unhurried and precise, which is respectful of the tissues and organs, reducing disease and post-operative complications to a minimum. The limitations of surgery have likewise retreated before the march of science: the lungs, heart, brain, and the large vessels, which not long ago were inaccessible, have become part of the realm of surgery that increases in daring and success day by day.

This advance in anaesthesia has been marked by many tentative procedures and has benefited from inspired discoveries. The use of ether quickly became general throughout the world (1846–1850). But soon chloroform (Simpson, 1847) came along to steal the limelight from ether, only to fall into disfavour later on because of its toxicity, resulting in syncope or serious damage to the liver. Soon the importance of adding oxygen to the anaesthetic gases was realized (Andrews, 1868). Emphasis was next placed on the freedom of the respiratory passages during anaesthesia: Trendelenburg, in 1869, made himself the champion of tracheotomy, and MacEwen, in 1878, proposed the insertion of a tube into the trachea through the vocal cords, which made possible a constant and easy control of anaesthesia as well as of oxygenation. The use of pre-anaesthetic medication, or premedication, goes back to Aubert in 1883; premedication usually involves a therapeutic combination, the effect of which is to produce calm in the patient, or indeed somnolence and euphoria, and at the same time to protect him completely from pre-operative and post-operative nervous reflexes. It also decreases the dose of the anaesthetic substances taken by the patient.

Anaesthesia performed by blocking nerve

conduction is called local or regional anaesthesia, according to what is required of it. This method goes back to the end of the nineteenth century. A special substance is placed in contact with a nerve or with the nerve endings, and the whole region normally innervated by these structures finds itself temporarily and reversibly isolated from the nervous system. By the use of this technique, the mechanism of which still remains partially obscure, it is possible to suspend either sensory or motor nerve functions, or both, in a whole region of the body. Cerebro-spinal and peridural anaesthetics are a particular instance of regional anaesthesia; the anaesthetic substance is introduced into the vertebral column inside or outside the dura mater (external meningeal membrane).

In 1874, Ore for the first time used intravenous anaesthesia by the injection of chloral. Since 1935, the introduction of quick-acting barbiturates of the pentothal type has ensured for this method a success which still continues.

In 1942, Griffith and Johnson, of Montreal, introduced curare into anaesthesia. This makes possible an operation which is helped by complete muscular relaxation combined with light—and therefore less toxic—anaesthesia and with artificial ventilation of the lungs. In 1950, Bigelow and his colleagues in Toronto described induced hypothermia in cardiac surgery.

## *Artificial hibernation*

It is well known that certain insectivores and rodents (marmot, hamster, hedgehog, squirrel) have the peculiar ability of lowering their body temperature and entering into a state of somnolence when winter approaches. This fall of temperature is accompanied by a slowing down of all the vital functions; metabolism decreases, the heart may beat only two or three times a minute, respiration hardly once a minute. This is natural hibernation.

It has seemed useful to reproduce this state of hibernation artificially in man. Certain surgical operations on the brain and heart sometimes require the circulation to be arrested for periods lasting from five to ten minutes; in a patient at 37° C this would cause irreversible injuries to the brain. But in man in a state of hypothermia, maintained, for example, at a temperature varying from 26° C to 30° C, the metabolism and the need for oxygen are reduced and surgical operation becomes possible. In the same way, in severe haemorrhagic or traumatic shock and in severe intoxications, hypothermia often makes it possible to avoid early death. This retarded life of the organs and tissues provides the time and protection necessary for the efficacy of the corrective treatment.

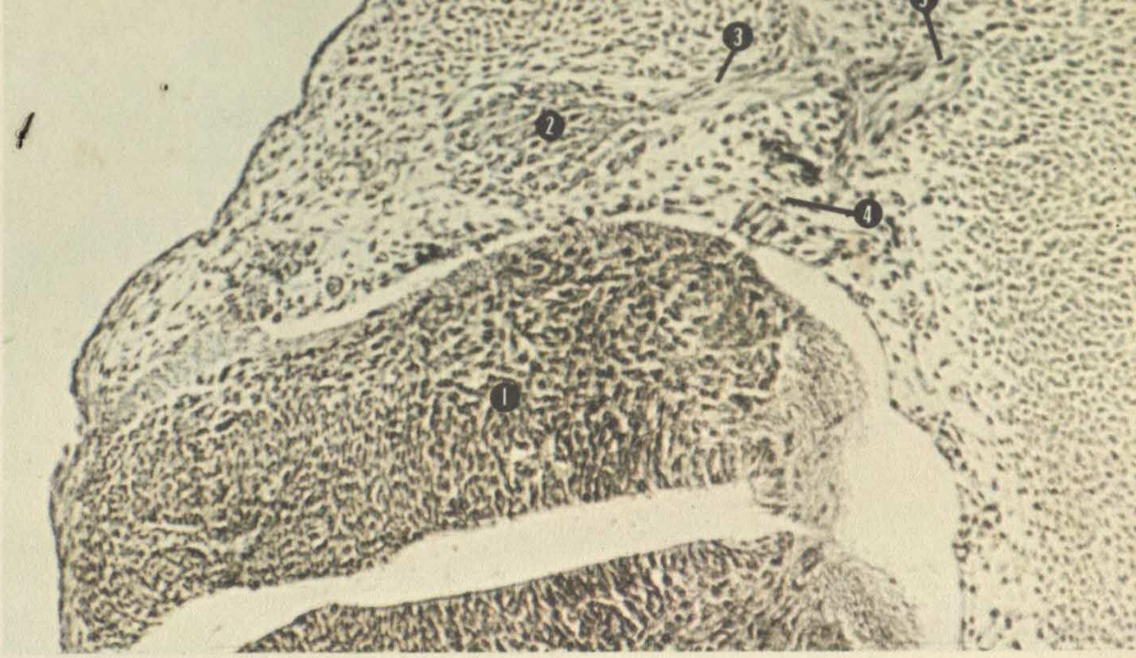

*Fig. 3. Section through the spinal cord of an eleven-day rat embryo. 1, spinal cord; 2, dorsal-root ganglion; 3, sensory nerve-fibres of the dorsal root running to the ganglion and the cord; 4, motor nerve-fibres of the ventral nerve-root issuing from the spinal cord; 5, mixed nerve conveying sensory and motor impulses. (Photo Lod, taken in the laboratory of Dr Oroux, Faculty of Medicine, Paris).*

The simplest and most widely-used method of lowering the temperature of the body is direct cooling of the skin. The patient is stripped and surrounded with ice-bags, or may even be enveloped in a refrigerating covering; this is done to bring down his temperature to about 30° C, which may take from forty-five minutes to three hours, according to the patient.

In addition to this, sedation or anaesthesia must be used to control the shivering which accompanies the cooling. Shivering doubles the consumption of oxygen. At the same time, it is necessary to avoid the constriction of the vessels, which retards the loss of warmth. It is also necessary to prevent the *stress* caused by the effects of the cold. Neuroleptics, especially largactil and lytic 'cocktails' (a combination of, for example, largactil demerol and phenergan) are among the drugs likely to be used. These cause vasodilation and also damp down the 'danger-reaction' by preventing shivering, decreasing muscular tone, and depress the temperature-control centre. All this takes place with a slowing down of the activities of the brain which is, in the circumstances, desirable.

It seems possible that in surgery, hibernation will be partially replaced by extracorporeal circulation. It will retain its value, however, in many of the most serious pathological conditions, the prognosis of which was almost always fatal as recently as fifteen years ago.

# Control of the general functions of the organism

### Fernand PLAS

It would be foolish to ignore the part played by automatism in voluntary movement and the part played by consciousness in the establishment and maintenance of automatic functions. Now, as everyone knows, good health requires a harmonious functioning of the body's various mechanisms and a man must strive to make that harmony right. From the moment he becomes aware of the functioning of his mechanisms he becomes to a certain degree master of their efficiency.

This conception, based on physiological data and on the observation of physical activities, forms the basis of training for sport and functional re-education.

We shall consider here successively the mechanisms of control of the four general functions: motor activity, circulatory activity, respiratory activity, and metabolism.

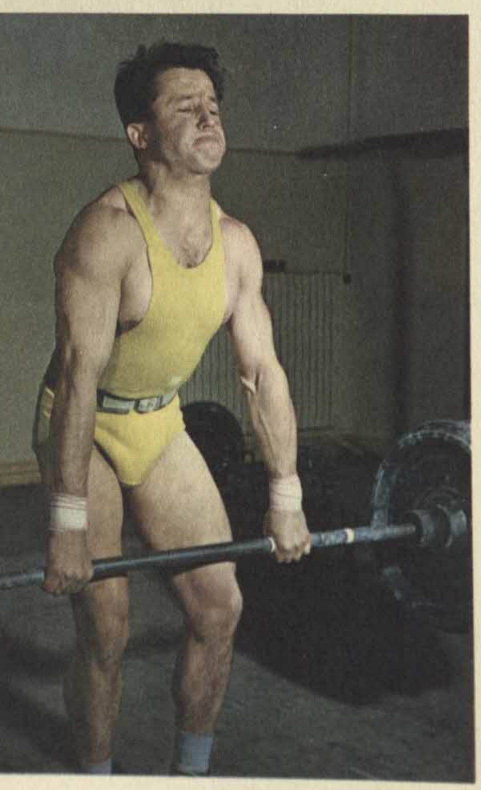

*Fig. 1. This example of the 'snatch' of. 90 kg shows how control of motor activity is exercised by means of suppleness of opposing muscles.*

## *Control of motor activity*

The movements that a man can make are of three kinds: reflex, automatic, and voluntary. The tissue through which they are executed is always the same one, muscle, but the processes that activate it are different. There is no precise limit between reflex, automatic, and voluntary movements, so one ought really to speak only of movements that are more automatic than voluntary or more voluntary than automatic. In man, the unique supremacy of the cerebral cortex dominates the problem of motor activity.

All movement is the result of an association between the sensory impressions and motor response. Automatic movement results from the coupling of sensory and motor impulses achieved by two organs: the thalamus and the nuclei in the central grey matter; voluntary movement results from a coupling of the motor area of the cerebral cortex and the sensory area; it is thus the outcome of a motor image.

'At the beginning of every voluntary movement, there is a mental picture of the movement which is usually unconscious and ignored, but is indispensable' (Chailley-Bert). This motor image is at first a visual representation of the gesture to be made. It consists chiefly of a bundle of kinaesthetic sensations that remain in the memory and derive from previous voluntary actions. In animals, these impressions are sufficient in themselves to set perfectly co-ordinated movements in motion: the sensation of lost equilibrium and the pressure of the air on the feathers are enough to ensure the flight of a pigeon, even when it has been deprived of the cerebral cortex (Flourens).

In man, in the left temporoparietal region, there are association areas in the vicinity of the anterior central gyrus which are the seat of motor images. If these areas are damaged, the mental picture of the movement is disturbed: although movement may be mechanically possible, it cannot be carried out; this is known as apraxia.

The sensations that affect this area are mainly those that originate from a stretching of the neuro-muscular spindles and from the excitation of the cells of Golgi in the tendons.

Every slightly complex movement seems like a very rapid succession of attitudes. In order that a movement may be made without fatigue or constraint, and so that it may be supple and precise, it is necessary that the automatism on which all the intermediate attitudes depend shall be as perfect as possible. The action of cortical control must be limited to the will to carry out the act and to its termination. All the intermediate links must be automatic. Perhaps this can be best understood by recollecting what it is like to try a sport, such as cycling or skiing, for the first time.

One of the aims of physical activity is to perfect one's automatisms by the repeated practice of certain exercises, so that the movements become precise. Greater efficiency and delay in the onset of fatigue will follow: hence the value of education in movement by practising a sport adapted to one's professional activities. To acquire such automatism it is necessary to acquire a perfect visual concept of the movement to be made and the best possible kinaesthetic image of it. Although a movement imperfectly executed may give a satisfying result, one should not be content with an imperfect performance, for it is easier to acquire a perfect automatism than to lose a defective one.

## *The various characteristics of physical activities*

Physical activities encourage suppleness, reliability, and strength of movement: suppleness depends essentially on harmony between opposing muscles (the flexors and extensors of a limb, for example) and on the contraction of one group working in smooth correlation with relaxation in the other, through reciprocal innervation (Sherrington). Poise is ensured by the stability of the joints, constantly maintained by the tone of the muscles, which are like active ligaments. Strength is directly related to the tone of the supporting tissues: the higher the tone, the greater the reserve of muscular strength and the less fatiguing the regular movements that are made.

This is particularly important when the motor power of a group of muscles has been damaged, as happens in acute anterior poliomyelitis. The muscle, which contracts as a whole, really consists of bundles of fibres that behave like functional units and constitute a motor unit together with an anterior horn cell in touch with the pyramidal tract and the motor nerve root that issues from it. A muscle is thus innervated by several motor roots. The work done by a muscle when a movement is made is effected by a larger or smaller number of motor units, according to the effort demanded, the effort itself depending on the weight of the part of the limb to be moved and the extent of the movement. In poliomyelitis, the activity of certain cell-groups is suspended or destroyed. When this happens it is important to develop the strength of those muscle fibres that are connected to motor cells which are still healthy. Passive movements are not enough to do this: active movements are essential. Hence the need for re-education to lessen the work demanded of the muscle, by reducing the resistance from the weight of the limb and by immersion or the use of supporting apparatus.

Education of the motor apparatus by means of physical activities must be adapted to the patient's age. Development of the supporting tone of muscular strength is useful only after the age of sixteen to eighteen. In adolescents it is necessary to develop skill and precision of movement. In children it is necessary to develop postural tone and to teach them to adopt and maintain a correct posture. A faulty posture causes fatigue because it provokes a conflict in the distribution of the postural tone, and in extreme cases may result in deformation of the bones. Elderly patients need exercises to maintain suppleness and keep them in good physical condition. But one should be careful. At fifty, the cardiovascular apparatus is no longer perfect and the desire to indulge in the sports of one's youth may, unless discernment is used, lead to serious consequences.

## *Control of circulation*

In studying blood movement (haemodynamics), it is of the utmost importance to know the output of the heart. The output per minute (the quantity of blood ejected by a ventricle per minute) is a function of the systolic flow and of the rhythm of the heart. The heart can quicken its output either by increasing the number of beats, the systolic flow remaining constant, or by increasing its expulsive force by emptying itself still further at each systole. Hearts that are well trained for physical effort increase their systolic flow.

At the time of making an effort the cardiac output, which is four to five litres when the body is at rest, easily reaches twenty litres. According to Wright, an output of forty litres would be the maximum output of which the heart is capable. This would correspond to an oxygen consumption of more than four litres per minute. This adaptation of output to oxygen requirements is not immediate. During the time needed to establish it, an oxygen debt is incurred which must be settled after the effort by the maintenance of cardiorespiratory functions. The quicker the adaptation, the smaller this debt will be. The speed of the adaptation of the circulation depends on the suppleness of the vascular system and on the state of the heart muscle.

When an effort is made, great disturbances occur in the vasomotor system. These changes, which are under the control of the vasomotor system, may be summarized as follows: the vessels of the muscles performing work undergo active vasodilation. This is caused in the muscle capillaries by the carbonic acid produced by the muscle cells and by acid metabolites. These metabolites cause dilation of the muscle arteries and of the principal arteries of the limb as a result of Fleisch's ascending nutrition reflexes (zonal reflexes). As long as the effort continues, this regional dilation persists. The area at work is thus isolated in a state of persistent vasodila-

*Figs. 2 and 3. Certainty of muscle tone and control of the joints: the bar is held at shoulder level. Strength: in direct correlation with the support tone, extension of the upper limbs, 'splitting' of the lower ones.*

tion into which the circulation stream pours. The coronary network benefits from this process, as also does the cerebral network, which shares in the increased circulation because of its virtual lack of vasomotor innervation. This vasomotor condition becomes independent of general vasomotor activity.

General vasomotor activity, controlled by central, mainly medullary, vasoconstrictor centres, tends to induce vasoconstriction. It is chiefly the carbonic acid entering into the general circulation, the acid metabolites resulting from muscular contraction, and adrenalin, that cause this increase in vasoconstriction.

*Fig. 4. In wrestling, skill and precision of movement are revealed: the wrestler, attacking his opponent from behind, is thrown on to the mat by a sudden forward flexure by his opponent, who has sunk to his knees. (Photo Lod).*

Thus the circulation flows evenly through the viscera and, during the first phase of effort, through the skin. The skin shows vasodilation only following a rise in body temperature and thus takes part in thermal regulation. Such circulatory oscillations have been well described by Dastre and Morat. They originate in the sluicing phenomena described by Jolyet and characterize the adaptation of the peripheral circulation during effort. Variations in blood pressure account for these vasomotor phenomena. When an effort is begun, the blood pressure undergoes variable oscillations; then, when the effort is at its height, the pressure becomes stabilized: the maximal pressure is considerably raised, values of 200 to 220 mm of mercury being usual. Such values show the importance of the phenomena of vasoconstriction, which are, however, restrained by the Cyon and Hering moderator nerves. The minimal pressure remains more stable, though it may show a slight rise, or sometimes a considerable fall, indicating the opening of new peripheral circulatory reservoirs. The differential pressure is then considerably increased. When in the course of an effort it begins to fall, this reduction is the first sign of fatigue. After effort, the arterial pressure very rapidly returns towards the lower values. It then continues to fall and it is often only twenty-four to forty-eight hours afterwards that it stabilizes itself. This shows the profound disturbance that the vasomotor apparatus undergoes during effort and the influence of physical activity on the vascular system.

## *Modifications of cardiac activity and rhythm*

At the same time as peripheral adaptation takes place, the heart also adapts itself. As Liljestrand, Nylin and Lindhart have shown, the systolic flow can be tripled at the moment of effort and may go from 40 to 120 ml; this occurs in spite of acceleration of the heart-beat. The mechanism by which this increase is brought about has not been elucidated. The critical threshold at which the systolic flow begins to decrease in an athlete's heart is at about 130–140 pulsations per minute. A factor in this adaptation is that the heart fills itself better because of the increase in the venous return. But Starling's law, which states that the greater output depends on the greater stretching of the heart-muscle fibres, does not apply in every case. In fact, the volume of the heart during effort is not increased during diastole. It is therefore necessary to conclude that in athletes there is an improvement in myocardial tone.

Physical exercise gives the heart a particular quality which reflects its characteristics. The heart of an athlete is large, slow, and sthenic.[1] The effect of training is to increase the volume of the heart. This increase is due to a hypertrophy of the heart muscle, shown by an increase in the weight of the heart, and to the dilation of its cavities. As a result, there is an increase in ventricular capacity. The rhythm of the heart is slowed down. At rest, the heart of an athlete has a rhythm of forty to sixty beats per minute. This bradycardia, which is of the sinus type, is a reflection of the hypertonicity of the vagus nerve which is set up by training. Long- and middle-distance running, cycling, rowing, and swimming are the sports most likely to develop this bradycardia.

Radiological examination of the heart during forced inspiration clearly shows the strength of vagal control and the force of the contractions thus obtained. Hence the interest in the re-education of cardiac patients suffering from valvular stenosis. This re-education is possible, provided that the heart can increase its output, that the heart muscle is not the seat of inflammatory lesions, and that the coronary circulation is perfect.

Learning to economize in one's movements reduces expenditure of effort, respiratory discipline improves lung ventilation, and the vagal hypertonicity regularizes and slows down the rhythm. By learning what it is possible for him to do, the young cardiac patient is able to master his affliction and a psychological equilibrium is established.

## *Control of respiratory function*

The respiratory function has the following peculiarity: its ventilation period is under a double control, automatic and voluntary.

Spontaneous ventilation, which depends on automatic regulation, is unconsciously directed by respiratory centres in such a way that the metabolism is ensured. This ventilation while the body is at rest is of the order of 4 to 5 litres per minute. When an effort is made, it can reach 50 litres, 100 litres, or even 120 litres, by increase in the frequency of respiration, which can be augmented from 12 to 16 respirations per minute to 30 or 40, and by increase in the volume of air inspired, which can be augmented from 500 cc at rest to 2 litres or more. But, while 500 cc represents the volume of tidal air, 2 litres represent the addition to the tidal volume of a part of the complementary air which is called the *respiratory reserve.*

## *Respiratory reserve*

The automatic regulation actuated by the simultaneous action of arterial carbon dioxide on the respiratory centres in the brain and by proprioceptive[2] stimuli coming from the joints and muscles is sufficient to produce these variations. But by bringing into play the accessory inspiratory and expiratory muscles one can considerably increase the ventilation: this testing of the maximal ventilation determines the maximal volume of air that the lung can handle in a unit of time.

The will can, moreover, control the respiratory rhythm by lengthening an inspiratory or expiratory period or by interposing phases of apnoea.[3] Methods of respiratory re-education are based on two principles: that of controlling the inspiratory and expiratory phases by exercises, and that of teaching the patient to make use of his accessory inspiratory and expiratory muscles and, by so doing, to substitute voluntary for automatic control, the object being to improve the ratio of fresh air to used air, which is the coefficient of lung ventilation.

But the volume of fresh air which enters the lungs at each inspiration is not entirely used for haematosis.[4] Of the 500 cc which constitute the tidal air, 150–170 cc remain in the dead space represented by the larynx, trachea, bronchi, and bronchioles. In establishing the coefficient of ventilation, therefore, the amount of this dead-space air must be deducted from that of the tidal air. The used air includes the expiratory reserve or reserve air (1 litre) and the residual volume or residual air (1·5 litres).

Let us suppose that a man's volume of used air is 2·5 litres and his tidal air 0·42 litre. He will normally need ten respiratory movements to renew the used air. But if he uses the respiratory reserve and breathes 0·84 litre each time (the volume of air in the dead space remaining unchanged), the volume of useful air will increase from 0·25 to 0·64 litre. At the same time, the increase of expiration decreases the reserve air and the volume of used air will be 2,300 litres. Under these conditions of ventilation three respiratory movements will be enough to renew all the air in the lungs. With equality of output in a unit of time, pulmonary ventilation will be performed better by the second type of respiration than by the first; hence the interest in respiratory gymnastics, which teach one to control the frequency and amplitude of respiratory movements during effort.

The efficiency of this increased ventilation is also a function of the capacity of alveolar haematosis. Now, during effort, haematosis is increased because some pulmonary capillaries, which are closed during periods of rest, are open to the pulmonary arterial blood. The pulmonary capillary flow increases during effort and this explains why the pulmonary capillary pressure remains constant in spite of a slight rise in the pulmonary arterial pressure. Thus, in spite of the reduction in the time during which the red blood corpuscles are in contact with alveolar gases (a period which, owing to the effect of the acceleration of circulation, decreases from 0·65 to 0·33 of a second) the maximum oxygenation of the red blood corpuscles is ensured. Thus a dynamic

*Fig. 5. The same wrestler avoids his shoulders touching the mat by 'bridging'; that is, by supporting himself on his head and feet: his opponent tries to break down this bridge. (Photo Lod).*

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(1) Sthenic *(from the Greek* sthenikos, *strong, active).*

(2) Proprioceptive stimuli *are stimuli proceeding from sense organs called proprioceptors, situated in the joints and tendons, which play an important part in posture.*

(3) Apnoea: *voluntary or involuntary arrest of ventilation of the lung.*

(4) Haematosis: *transformation of venous blood into arterial blood in the respiratory apparatus.*

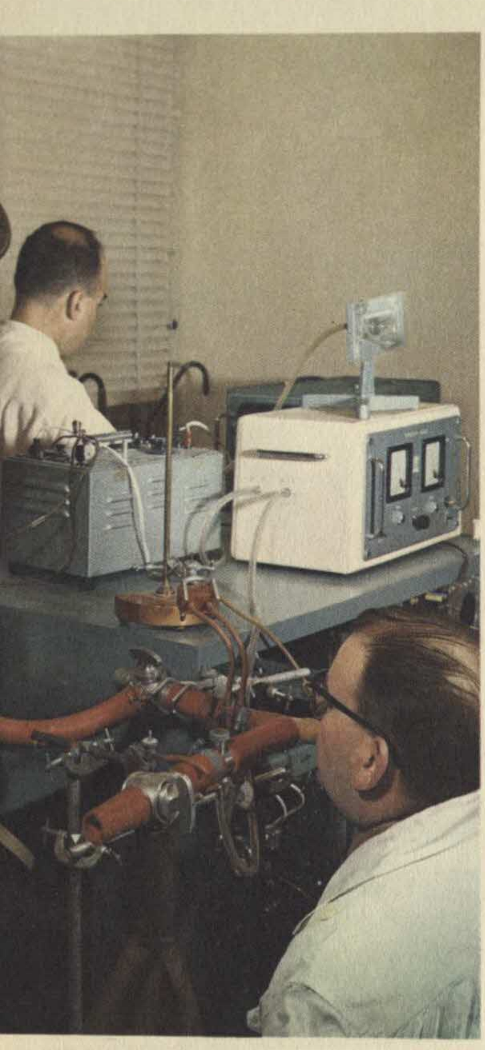


*Fig. 6. Investigation of respiratory function: measurement of functional residual capacity with the help of a nitrogen analyzer. (Photo Lod, taken at the Centre d'Études et de Recherches de Médecine Aéronautique).*

effort makes it possible to achieve ventilation conditions and a pulmonary circulation that are very favourable to haematosis. One must not therefore minimize the possibilities of respiratory re-education in a normal person: respiratory re-education retrogresses the moment breathlessness occurs. In pathological cases, not only those who suffer from deficient respiration, such as asthmatics, but also those who are afflicted by the premonitory syndrome of a chronic pulmonary heart, should benefit from respiratory re-education, which is likewise the most useful treatment for acute cases of cardiac insufficiency.

## *Control of metabolism*

The study of variations in the consumption of oxygen and the production of carbon dioxide shows the volume attained by metabolic phenomena during muscular exercise. A man at rest will consume 200 to 250 cc of oxygen per minute and produce 200 cc of carbon dioxide. During a violent effort he can consume four litres of oxygen and produce five litres of carbon dioxide. As a practical example, a walk at the rate of 8 km (5 miles) per hour requires the consumption of 2·5 litres of oxygen per minute and the excretion of 2·4 litres of carbon dioxide.

Effort increases catabolism and is followed by respiratory anabolism. But during prolonged efforts catabolism and anabolism occur together. Excretory products increase in the blood: on the one hand, lactic acid, which is evidence of carbohydrate catabolism, and, on the other, urea and uric acid, which are evidence of protein catabolism. Lactic acid may increase from 150 mg per litre to 2 g per litre; nitrogenous excretory products in the blood (azotaemia) increase from 0·3 to 0·9 g. There is therefore an increase of carbohydrate and protein catabolism, which partly depends on the increase in the secretions of the suprarenal cortex. In fact, the elimination in the urine of the total corticoid-reducing agents and of the 17-hydroxycorticoids is markedly increased. But the simultaneous marked increase in the elimination of the 17-ketosteroids (which provide information about the anabolizing androgen hormones) is evidence of the speed and intensity of the reparatory process. Training for sport induces increased function of the suprarenal cortex, which plays its part in maintaining the good condition of connective tissue. When a person in training is examined and tested periodically for the same effort, it is found that oxygen consumption decreases after a few days (Brouha), as if the effort required resulted in a smaller expenditure. Then, paradoxically, it increases again. The study of the lactates in the blood provides the explanation of this phenomenon; the lactate level continues to fall. The person who is training benefits from a more efficient combustion and the effort helps the oxidation-reduction processes which characterize life.

It may also be noted that blood cholesterol is less abundant in athletes than in persons who are sedentary, a fact which has a certain interest for the prevention of atherosclerosis. It is interesting to recall in connection with this, the work of De Lannes on the migration of proteins during effort. It is known that in a state of rest there are exchanges between the blood plasma and the interstitial fluids, not only of water and minerals, but also of proteins. During an effort, the large molecules of the protein fractions have considerable difficulty in filtering through, the result being that the β globulins diffuse more easily into the intercellular spaces than the α1 and α2 globulins. After the effort, their value remains lowered, as if they had been consumed on the spot. Certain experts see in this a proof of the efficacy of physical activities in preventing atherosclerosis.

But these effects on the metabolism have a drawback. Sedentary people who already have a faulty metabolism and a deficient renal function should beware of taking vigorous exercise. The occurrence of gout after athletic exercise is an example of what may happen, which is not surprising, because the increase of uric acid in the blood after effort is well known.

Physical exercise is the best means of obtaining the highest efficiency in our physiological equipment. But such exercise must be adapted to one's age. The young will aim to develop strength and harmony of movement. Their elders must be content with preserving their suppleness and remaining in good condition, which will depend on maintaining the oxidation-reduction potential which is the basis of all metabolism.

Thus by a discipline voluntarily accepted, man can to a certain extent direct the physiological systems that seem to escape the control of the will. But this control is not without effect on the vago-sympathetic system. Circulatory, respiratory, and nutritional reactive habits are induced, from which a healthy man benefits and which the sick can adopt to re-educate themselves. These habits in turn influence the mind and thus establish a harmonious psychosomatic equilibrium.

# Painless childbirth

### Tove SCHMIDT

Over the years, great changes have taken place in obstetrics and intensive efforts have been made to improve the conditions of pregnant women and women in labour, so that today danger to both mother and child is reduced to a minimum.

Nowadays, much more importance is attached to prenatal examinations than in the past, and thanks to these examinations serious complications are often avoided. Confinement in hospital, which is now much more common, the use of antibiotics, improvements in anaesthetic techniques and in facilities for blood transfusions, mean that today mothers and children can be saved in situations that would formerly have been regarded as hopeless.

As the history of medicine is bound up with the fight against pain, there has naturally always been an interest in the pains of childbirth. The earliest attempts to overcome them were made with sedatives based on morphine. The first confinement in which anaesthesia was used was that of Queen Victoria, who was given chloroform while she was in labour.[1] During the last fifty years, a number of less dangerous anaesthetics have appeared, but none has proved entirely effective and in most cases their use has had disadvantages for either the mother or the child.

Ideally, an anaesthetic used in obstetrics must fulfil the following conditions: one, it must prevent all pain; two, it must not diminish the strength of the contractions, which would hinder the normal course of the birth; and three, it must not harm the child's respiratory system. Only during the last thirty years has it come to be recognized that as a result of prenatal psychological preparation, and the realization that labour must be suitably controlled, these conditions would be met. It is well known that glandular activity and the working of the smooth and striated muscles can be influenced psychologically; for example, by something one remembers, by fear of the unknown, a desire to excel, or a surrounding atmosphere of turmoil.

We do not know in exactly what way psychology plays a part in these matters, but the autonomic nervous system[2] is thought to be a determining factor. As all midwives know, the course that childbirth takes depends largely on the psychological condition of the woman in labour. A calm, confident woman who has decided to co-operate will give birth much more easily than one who is agitated or distressed. Understanding of this has helped in the perfection of methods of 'natural childbirth' by relaxation or by psychoprophylaxis. These methods are based on educating future mothers in the practice of relaxation and in a special method of breathing. It also calls for the constant and friendly presence of a qualified midwife or nurse to reassure the woman in labour.

From 1933 onwards, the British obstetrician, Dr Grantly Dick-Read, began his experiments with 'natural childbirth'; ie, childbirth without the use of sedatives, the mother-to-be having been psychologically prepared during pregnancy and continuously helped by a competent person during the birth. This method has since made considerable headway throughout Europe. Dr. Dick-Read published an account of his experiments in a celebrated book *Childbirth Without Fear* (Heinemann, London, 1935). His theory has been summed up thus: ignorance engenders fear; fear causes muscle tension; muscle tension causes pain; whereas knowledge brings tranquillity of mind; tranquillity of mind brings calm and physical relaxation and prevents the onset of pain.

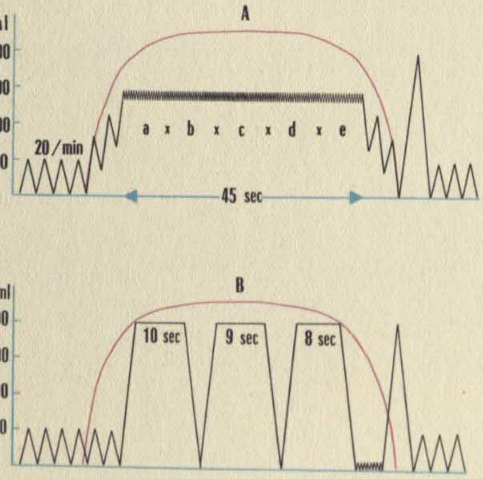
Education of expectant mothers should should therefore include theoretical instruction on the normal stages of childbirth, combined with practical exercises in relaxation and reduction in muscular tension.

It is only since 1952 that the practice of painless childbirth as a result of psychoprophylaxis has made headway in Europe, under the championship of the French physician Fernand Lamaze, who introduced it systematically at the Pierre-Rouquès Clinic in Paris.

The psychoprophylactic method of painless childbirth is based on the Pavlovian theory of conditioned reflexes. In 1912, Pavlov succeeded in demonstrating that a reflex—in this case the salivary secretion of a dog, which is an unconditioned reflex—can be induced

(1) *Hence the expression 'the Queen's chloroform'; the practice is still widespread during the expulsion stage.*

(2) Autonomic nervous system: *that which governs the visceral and involuntary functions; it is composed of ganglia and nerves and is connected to the spinal cord in which the reflex centres are situated. The autonomic system includes the sympathetic and parasympathetic systems, which innervate the same organs and have antagonistic effects.*



*Figs. 1 and 2. The upper curve represents a contraction (45 secs). In A, during the period of dilation, the rhythm of respiration follows the intensity of the contraction. In B, during the period of delivery, three expulsive efforts are possible while the contraction is at its maximum intensity.*

simply by external stimulation of the cerebral cortex; that is to say, an unconditioned reflex can be transformed into a conditioned reflex. This principle has been developed since 1920 by the Russians Platinov, Velovski, Plotitchev, Chougom, and Nicolaiev, who have shown how the defensive unconditioned reflex of uterine contraction in women can be transformed into a conditioned reflex of breathing; in other words, the negative attitude of a woman in childbirth can be transformed into a positive one.

A woman who is ignorant of what will happen during the birth of her child, and who has always heard it said that birth is inevitably accompanied by excruciating pains, becomes panic-stricken and releases a series of defensive reflexes: she cries out and contracts her muscles, especially those of the pelvis; the functions of the central nervous system are disturbed, resulting in an upset of the activity of the uterus that takes the form of uncoordinated contractions, spasms[3] of cervix and uterus, inertia, etc. But a woman who has been prepared and who realizes that the contractions, by causing dilation of the cervix, bring about the expulsion and delivery of the child, reduces the excitation of her cerebral cortex, remains calm, shows no defensive reflexes, and does not hinder the normal course of childbirth.

Excitation of the cerebral cortex caused by contractions can also be avoided by the practice of a simple breathing technique, which is automatically adopted when the contraction appears and is maintained as long as it lasts.

At the beginning of the dilation stage, when the dilation measures no more than the width of one or two fingers, the woman breathes deeply and regularly (fig. 1). During this stage she need not remain in bed, but can undertake light manual work which will keep her occupied—knitting, for example.

During the second stage of dilation, which lasts until the cervix has become completely dilated, she increases the amount of air in her lungs by breathing two or three times as soon as she feels the contraction beginning. Throughout the contraction, she should breathe quickly and superficially, and more quickly as the contraction becomes stronger. This superficial breathing can be compared to that of a running dog. As the contraction decreases, she reduces the amount of air in her lungs until, after two or three breaths, she breathes in normal amounts and then continues to breathe regularly until the next contraction. In this stage of labour the woman should lie extended on her side in a relaxed position.

During the stage of the child's expulsion, her attention will be concentrated on the effort of pressure that is required of her (fig. 2).

When the contraction reaches its maximum, she should breathe in deeply, hold her breath and bear down for about ten seconds, then breathe out deeply, breathe in again deeply, hold her breath, bear down, etc, the whole sequence being repeated three or four times. As the intensity of the contraction decreases, she should breathe out deeply and then continue to breathe in a panting manner until the contraction has entirely ceased, ending with one deep breath—in and out. In this way the strength of the expulsion can be controlled all the time by alternately pressing and panting; this is extremely important at the moment when the child's head appears. Thus the woman co-operates throughout the delivery. This presupposes that her threshold of sensitivity is increased to its maximum and that the excitation caused by the contraction will not overstep this threshold.

Although the first and third requirements of an anaesthetic have long been understood, it is only from the end of the last century that attempts have been made to overcome the problems of the second by using spasmolytic,[4] analgesic,[5] and anaesthetic[6] preparations, which unfortunately often make the woman incapable of effective co-operation.

The use of oxygen and the methodical rupture of the amnion as soon as the dilation has reached three fingers' width are also important in the psychoprophylactic method. Oxygen administered between the contractions has a stimulating and slightly analgesic effect on the mother and at the same time helps to avoid anoxia in the child.

Nowadays, a woman can and ought to learn to bring her child into the world with the same care that she shows in attending the doctor or the clinic for prenatal examinations. Now that both methods—the psychoprophylactic method and that of Dr Dick-Read—have been tried for a considerable time and in most parts of the world, the psychoprophylactic method appears to be generally preferred.

Preparation is carried out in small groups of five or six, who meet once a week after the sixth month of pregnancy. Each course consists of a theoretical lecture lasting forty minutes, followed by exercises in neuromuscular control. This physical training is aimed particularly at those parts of the body directly concerned in parturition, combined with exercise in the different techniques for the control of breathing.

A midwife instructing patients either individually or in groups—and incidentally it is a good thing for pregnant women to mix with one another—might well plan her system of instruction on the following lines:

First lecture: normal pregnancy, diet for pregnant women, and a brief description of normal childbirth.

Second lecture: summary of the psychoprophylactic method; conditioned reflexes and superficial breathing.

Third lecture: details of the dilation stage and the importance of superficial breathing during this phase.

Fourth lecture: details of the expulsion stage; exercises in pressing and breathing during expulsion.

Fifth lecture: introduction to breast feeding.

Sixth and seventh lectures: general revision; answers to questions; how to recognize the beginning of labour; going to the hospital in good time, the various things needed there, etc.

The principles of neuro-muscular education are:

1. To teach the patient which are the muscles that she will have to use during the birth, and how to use them to best effect.

2. To teach her which are the muscles that should not be brought into use during labour, but should on the contrary remain relaxed and at rest, so as not to interfere with labour.

In short, expectant mothers should learn how to conserve their strength so as to be able to overcome exhaustion, a great danger during childbirth. During the courses of exercise, there should be frequent repetition of the various respiratory techniques, so that they may become similar to conditioned reflexes, started automatically when contractions begin in the patients. Finally, attention should be paid to periods of rest, and expectant mothers should learn to relax in correct positions which they will adopt during the period of dilation.

In very large hospitals it is impossible to give instruction to all pregnant women, nor is it any longer absolutely necessary to do so, because many women give birth successfully without prenatal preparation, provided that a qualified person is present to guide them during labour. However, it is usual to offer instruction to every woman who needs it. The ideal would be to give such instruction to every primipara, and for the multiparas to attend one or two refresher courses. There would thus be a gradual change in the attitude of the public to childbirth.

In 1958, an experiment was undertaken in Copenhagen in order to estimate the value of the psychoprophylactic method. A comparison was made between ninety women who had given birth using this method and ninety-seven who had given birth without such preparation. The latter were helped with trilene. All of them were normal primiparas, who had had children weighing at least 6 lb, born by occipital presentation without mechanical hindrance.

In the first group the period of dilation was shorter than in the second. In 87 per cent of the women in the first group the period lasted less than twelve hours, while this applied to only 61 per cent of the women in the second group. Moreover, of the first group, 73 per cent gave birth in less than twelve hours without any help other than the respiratory exercises they had learnt in advance; whereas of the second group, who were helped only with trilene, only 48 per cent gave birth within twelve hours. In the first group the heart-beats of the foetus were not disturbed in a single case and none of the newly-born children came into the world in need of resuscitation. In the second group, however, the heart-beats were disturbed in nine cases and two children had to be resuscitated.

The duration of the expulsion stage, the number of forceps cases, and the frequency of puerperal infection was the same in both groups, as also was the delivery.

Thus we see that preparation of the pregnant woman for natural childbirth has not revolutionized obstetrics in the sense that it has diminished the number of obstetric complications, but it has become an essential element for successful childbirth. But not all women should be compelled to use the natural method of childbirth, because in the course of labour difficult moments may occur in which nitrous oxide or trilene will be a temporary help, and their use will not deprive the mother of the joy of seeing the birth of her child.

It is wrong to believe that one can achieve painless childbirth just as one can pass or fail an examination. To 'learn to give birth' simply means making sure as far as possible that all will go well. There is no doubt that normal childbirth proceeds much more easily both for mother and child by natural methods than with the use of sedatives or analgesic anaesthesia.

(3) Spasm: *an involuntary contraction of a group of muscles or of one muscle, or of an isolated bundle of muscle fibres. Here it means complete contraction of the uterus and cervix.*

(4) Spasmolysis: *elimination or reduction of a spasm.*

(5) Analgesia: *abolition of sensitivity to pain.*

(6) Anaesthesia: *general or partial deprivation of general sensitivity or of the sensitivity of an organ.*

# Allergy and desensitization

*Bernard N. HALPERN*

*The correction of regulatory disturbances caused by hypersensitivity is here studied by a master of the subject, Professor Bernard Halpern, who considers every aspect of the problem, biochemical, pharmacological, physiological, and therapeutic. There is a special discipline of medicine for the study and treatment of hypersensitivity diseases. But even though the manifestations of excessive sensitivity are episodic and often slight, the real reason for the disturbance lies deeper and is probably dependent on heredity.*

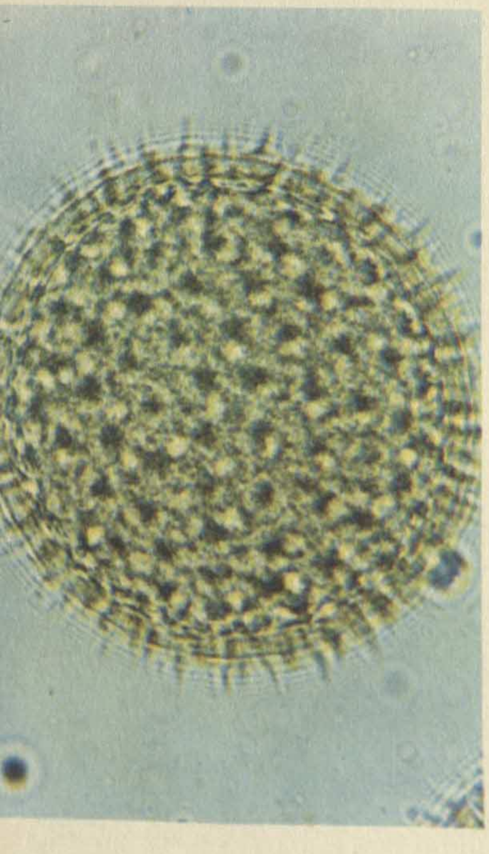


*Fig. 1. A grain of pollen highly magnified. (Photo Lod).*

Allergy, known until not long ago as idiosyncrasy, first appeared officially in 1907, when it was introduced by the Viennese pediatrician, Clemens von Pirquet. Von Pirquet used the word, which means 'impaired reaction', to designate certain biological and clinical phenomena that include Richet's and Portier's experimental anaphylaxis (1902), the pathological reactions observed in patients after the injection of therapeutic sera of heterogeneous origin,[1] and the hypersensitivity reactions to tuberculin in individuals who have a tuberculous infection.

The term allergy was soon adopted by immunological and medical authorities and its significance has been progressively extended. Today, it includes many pathological symptoms, clinically and histologically rather dissimilar, which are, however, conditioned by the same immunological process.

In medicine, allergy embraces a series of more or less serious diseases, among which the better known are hay fever, spasmodic coryza, asthma, certain eye affections, urticaria, Quincke's oedema, some forms of eczema, certain blood disorders, and various affections of the digestive tract, the kidneys, vessels, etc.

In proportion, as our knowledge of the biochemical nature of allergic states increases, we perceive that other disorders ensue from the same process—known as hypersensitivity, notably, acute articular rheumatism, disseminated lupus erythematosus, certain disorders of the nervous system, the collagen diseases, etc., and those mechanisms that intervene in the elimination and rejection of a tissue graft or of an organ (even if the graft is derived from an individual of the same species or from the same family, except in the case of monozygotic twins).

The hypersensitivity reactions have very extensive significance. They control the maintenance of the specificity of the individual and of the species. Their mechanism has been explained in the preceding volume.[2] In the present chapter we shall therefore concentrate on clinical allergic syndromes.

## Factors which condition the state of allergy

Potentially, every individual can become allergic. In fact, 30–40 per cent of the people of white races are affected during their lives by a condition of allergy of longer or shorter duration. It is estimated that 10 per cent of the white races are affected by various types of major and persistent allergy.

The factors that condition the appearance and establishment of an allergy are either endogenous or exogenous.

*(a) Endogenous factors* include the totality of the organic and psychological factors, comprised in the vague term 'background'.

Among the endogenous factors is hereditary predisposition. Although this has not been demonstrated with certainty, statisticians agree in recognizing that genetic factors control the hereditary transmission of the liability to contract clinical allergic disorders that arise from the group of direct hypersensitivity allergies. This form of transmission appears to be due to the presence in the chromosomes of a dominant gene.

The state of the skin and mucous membranes is also an important factor. Mucous membranes that are chronically infected or irritated, or a dry, fissured skin deprived of its film of fatty-acid, facilitates the entry of antigens.

Gastro-intestinal infections and irritations likewise facilitate the penetration in large quantities of food proteins, ie, of substances that are highly antigenic.

Although psychological factors are often evoked in both scientific and non-scientific literature, the part they play has still to be determined.[3]

*(b) Exogenous factors* include, above all, climatic and environmental conditions. It is well known that there are more serious cases of asthma in countries with a humid and misty climate than in those that are dry and sunny. The percentage of asthmatics in mountainous countries is very low in comparison with the percentage of those living in the plains. Climate, of course, includes not only sunshine, the nature of the soil and the humidity, but also vegetation. The allergenic, harmful properties of vegetable emanations vary with their botanical nature. A typical example is furnished by sensitivity to pollens. In the United States, 7 per cent of the population are sensitive to the pollens of grasses, and 4–5 per cent show clinical allergy to the pollen of ragweed *(Ambrosia trifida)*.

The antigenic power of substances of vegetable origin which may affect the skin is likewise variable according to the nature of the plant. *Rhus toxicondendrum*, commonly called *poison ivy*,[4] contains an oleoresin endowed with a considerable sensitizing power; 95 per cent of individuals are sensitized to this plant by simple contact. The primula, the artichoke, and the castor-oil bean are all equally responsible for numerous cases of skin allergy, although their sensitizing properties may be much less marked.

Certain professions predispose those engaged in them to allergenic sensitization more than others because of the chemical nature of the substances that are handled. Among furriers, bakers, and seedsmen, the percentage of asthmatics is especially high; eczematous skin diseases occur frequently among hairdressers, dyers, dentists, and furriers. This is due to their handling of products containing an $NH_2$ radical in the para position.[5]

These examples show how complex the process of hypersensitivity is. It is true that experiments performed on animals have made it possible to analyze the sequence of these phenomena and to determine their immunological nature. But diseases produced in animals are not entirely transposable into clinical syndromes, though progress is made possible by the simultaneous confrontation of the two kinds of information.

## Treatment of allergic disorders

Because of the nature and development of allergic affections and of the conditions under which they appear, treatment of them cannot be uniform. There are three points to be considered here: *(a)* prophylactic measures; *(b)* neutralization of the phenomena of hypersensitivity; *(c)* methods of desensitization and specific antagonists of histamine.

## Prophylactic measures

Great importance attaches to prophylactic measures against allergic disorders. These measures are necessary from birth onwards. The room in which a child lives should be clean, well-ventilated, sunny and without velvet hangings or carpets. Dust should be removed by a vacuum cleaner while the child is out of the room. Baby-clothes should be made of cotton because direct contact between the skin and wool may cause sensitization. For the same reason, synthetic textiles and feathers should be eliminated. Animals such as dogs and cats should preferably be kept at a distance. For washing, bland soaps and mineral powders should be used and complex medicated powders excluded. Ointments, lotions, and eye drops may be used in modera-

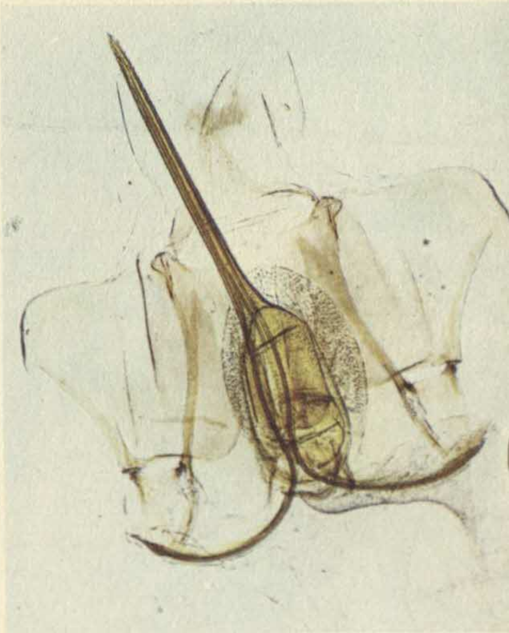


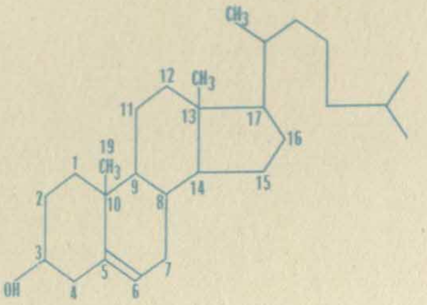
*Fig. 2. The sting of the bee contains a poison which acts in sensitized persons like an allergen and causes an allergic reaction.*

(1) Heterogeneous: *derived from a foreign organism.*

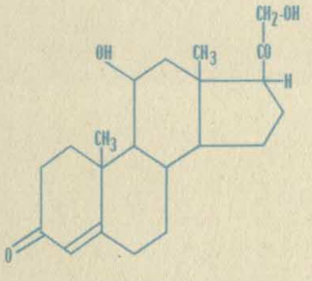
(2) Hypersensitivity. *Raoul Kourilsky, page 48, Volume VI.*

(3) *Investigation into this aspect of the subject has recently been undertaken for asthma. It is described in Volume 6. It establishes the fact that the control of psychological conflict has a powerful effect on the intensity of the symptoms and on their renewal. (R. Kourilsky).*

(4) Poison ivy: *a plant very common in certain parts of North America; contact with it causes dangerous burns on the skin.*

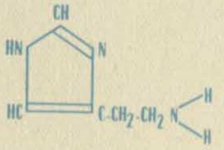


cholesterol



corticosterone

*Fig. 3. Cortisone, the hormone secreted by the cortex of the suprarenal gland, is commonly used to neutralize the effects of hypersensitivity.*



β-ethyl imidazoline

*Fig. 4. β-ethyl-imidazoline, better known as histamine. This plays a determining part in allergic phenomena.*

*Opposite page. The diagnosis of hypersensitivity is made by injecting the suspected allergen under the skin. If there is an allergy to it, a papule appears twenty minutes after the inoculation. This photograph shows a histological section of one such papule (above and to the right). The skin was removed for examination four hours after the injection of the mould* $1P^2$. *An inflammatory reaction (more deeply coloured) has been produced round the papule. (Mag. ×100). (Photo Lod).*

tion. Careful watch must be kept for rhinopharyngeal infections, which should be treated promptly without placing too much trust on local treatment. Similarly, all likely causes of skin irritation are to be avoided, such as detergents and organic antiseptics. An inflamed digestive mucous membrane permits ten to twenty times more proteins (ie, formidable antigens) to pass through it than does a healthy one; the state of the digestion will therefore need careful supervision.

For anyone suffering from an allergy, housing can be a big problem. Statistics have shown that the number of serious cases of asthma is greater in damp and foggy regions, and on clay soils where moulds flourish in houses, than in sunny regions with permeable soils or in mountainous countries. The choice of a profession can also be a cause of trouble, which may mean taking into account the nature and conditions of the work. Asthmatic adolescents, or those whose forbears were asthmatic, would do well to avoid becoming bakers, seedsmen, millers, furriers, plasterers, etc. Likewise, people whose skin is sensitive or who have had eczema should be advised against becoming hairdressers, dyers, furriers or dentists.

Ordinary vaccination of allergic children must be carried out with care. Those suffering from chronic eczema should not be vaccinated against smallpox. Other vaccinations must be done with caution or when there is no acute allergy.

Drugs, even the simplest, as well as those most in use, can be dangerous allergens. If, after the use of a drug, an abnormal cutaneous, respiratory, febrile or digestive reaction appears, that particular drug must be set aside; if the reaction shows itself as urticaria, oedema, eczema, or asthma, the drug must not be given again under any circumstances.

## *Neutralization of hypersensitivity*

This chapter deals only with non-specific symptomatic treatment. Therapeutic treatment, either symptomatic or immunological, will be outlined subsequently.

Allergic reactions can show dramatic symptoms and may demand urgent treatment. The most striking reaction is anaphylactic shock following the injection of a therapeutic serum (anti-diphtheria, anti-tetanus, etc) or the injection of an allergen or of certain medicines, such as penicillin or procaine; even the sting of a wasp or a bee (fig. 2) can be serious in a sensitized person. The symptoms appear within minutes of the injection, which may produce a state of syncope with cardiovascular collapse, followed in extreme cases by death.

Sometimes the symptoms show themselves by a massive attack of urticaria with congestion of the mucous membranes and asthmatic suffocation.

The classic treatment for these alarming conditions is *adrenalin*. Given subcutaneously, it can, by its powerful cardiovascular effects, retrieve in a few minutes situations that may seem desperate. In most cases it is necessary to give another drug with adrenalin, such as one of the synthetic antihistamines.

A relatively recent advance is in the use of *pituitary and suprarenal hormones* in allergic disorders. Either the anterior pituitary hormone, ACTH is used (its property is to stimulate the secretion of the hormones of the suprarenal cortex) or steroid hormones, secreted by the cells of the suprarenal cortex, notably cortisone, hydrocortisone and their synthetic derivatives, prednisone, hexadecadrol and triamcinolone.

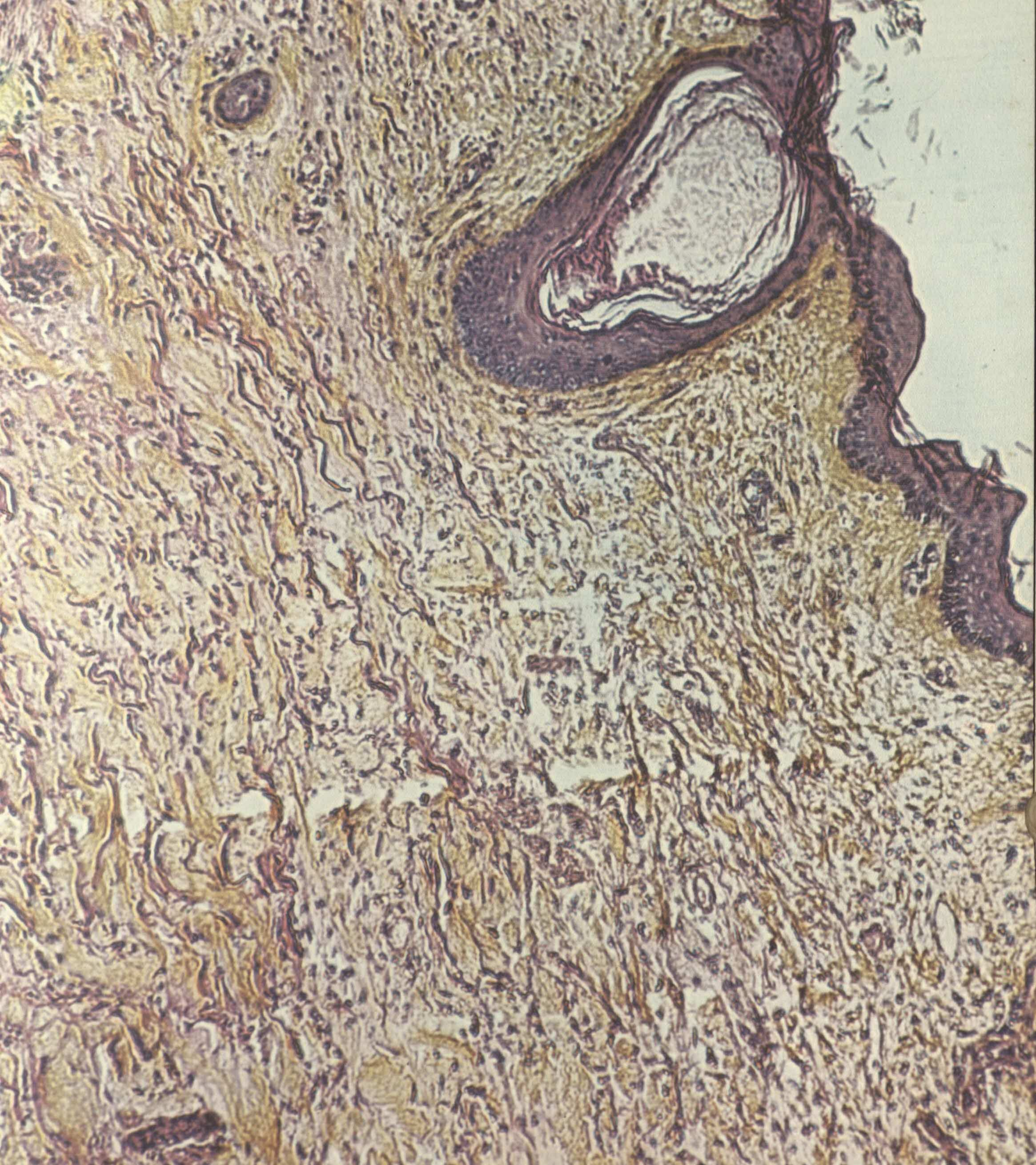
ACTH is a polypeptide hormone and because of this it is attacked by digestive ferments. It should be given parenterally, though usually it is given intramuscularly; slow intravenous injections are used in urgent cases. Its action does not last long because it is rapidly eliminated, so ACTH is incorporated in a gel which takes several days to become absorbed.

Cortisone and its derivatives, which are hormones derived from sterol (fig. 3), are well absorbed from the digestive tract; the usual method of administering them is by mouth.

ACTH and the hormones of the suprarenal cortex act on allergic phenomena in a remarkable way. The respiratory and cutaneous symptoms disappear more or less completely after a few hours and the patient feels almost miraculously cured. Unfortunately, this improvement seldom lasts for long, and when the treatment is discontinued, the symptoms reappear and are almost as intense as before.

The administration of hormones must be strictly supervized because they may cause severe metabolic troubles, such as salt and water retention, osteoporosis, gastroduodenal ulceration, psychological troubles, and disturbances of carbohydrate metabolism.

How do the hormones act? The mechanism of their action has not yet been fully worked out. It is known that they can diminish



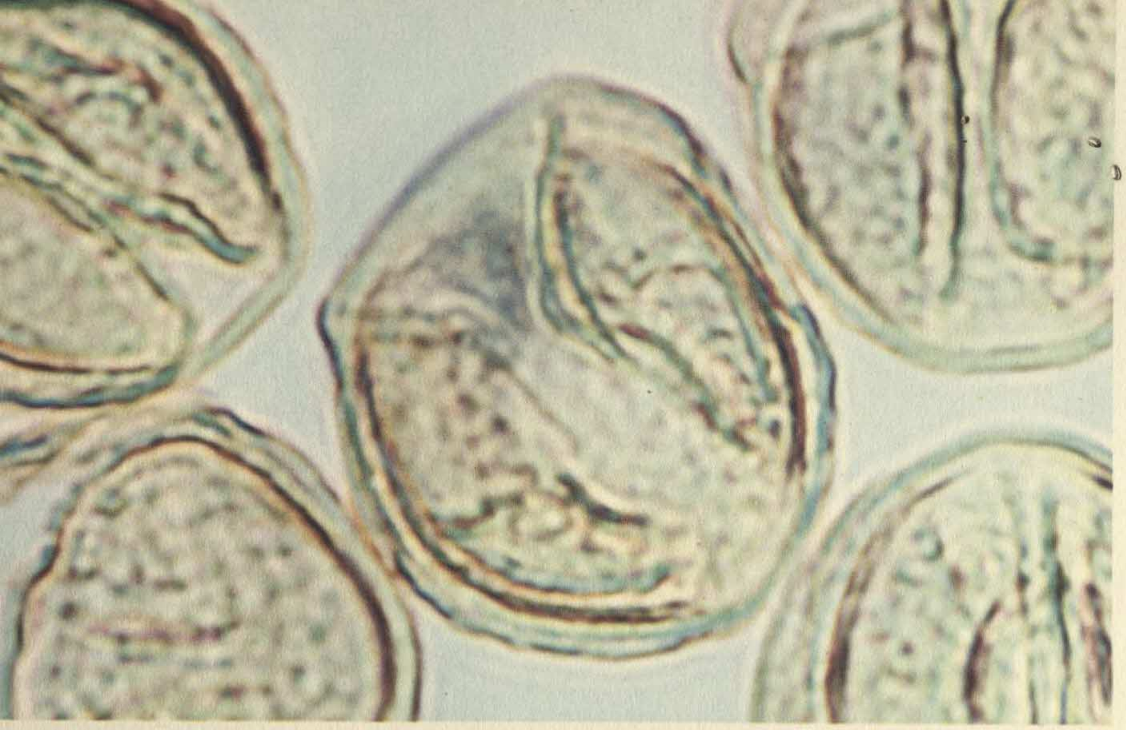
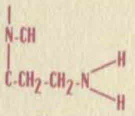
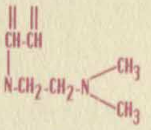


*Fig. 5. Pollen grains seen through the microscope. (Photo Lod).*



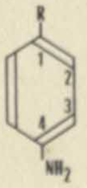
histamine



antihistamine

*Fig. 6. The chemically active radical of histamine and antihistamine.*

[5] *Note the relation between the chemical constitution and the allergenic power of chemical substances. Thus, in the group of aromatic amines, the antigenic power of substances in which the amino group is in the para position (position 1–4) is considerably greater than that of substances in which the amine is in the ortho position (position 1–2) or the meta position (position 1–3):*



all inflammatory processes, whether these are allergic or not.

The recent work of Professor Halpern and his colleagues has shown that cortisone and its derivatives inhibit new formation of endogenous histamine. It is possible that the neutralization of allergic phenomena may be associated with the inhibition of the synthesis of histamine by these hormones. But it is almost certain that their effects on the metabolism of histamine constitutes only one aspect of their anti-allergic activity.

## Histamine and antihistamines

We have seen that the chain of immunological reactions which leads to clinical disorders originates in the union between the antigen and the antibody, and that the outcome of it is the liberation of histamine. But what is histamine?

It is a substance which is of prime importance in the production of allergy and is known to chemists as β-ethyl-imidazoline (fig. 4). This basic amine, which has had a long and exciting history, has not yet yielded all its secrets.

It has a considerable toxicity for most mammals—0·25 mg will kill an adult guinea-pig. Yet, if one were to assess the amounts of histamine present in the tissues of mammals, including man, the result would be startling; it would amount to several dozens of fatal doses.

How is this paradox explained? The answer is that histamine is found in the cells in the form of an inactive precursor. It becomes dangerous only when it is discharged in its free form into the tissue fluids. This is what happens in allergic phenomena. Thus allergic phenomena arise from the reactions between the antigen and the antibody and, as the final feature of this reaction, the liberation of histamine into the tissues.

It was the British scientist, Sir Henry Dale, who put forward this hypothesis in 1910. Since then, it has frequently been confirmed. The boldness of this idea is shown by the fact that when this hypothesis was formulated the presence of histamine was only a conjecture.

Histamine is one of those chemical tools that the organism uses either to ensure physiological functions or to start pathological disorders. It is remarkable that no real antagonist to histamine exists among natural products. In 1937, D. Bovet and A. M. Staub, of the Pasteur Institute in Paris, found for the first time synthetic substances which had antihistaminic properties. But these substances were unusable because of their toxicity. In 1942, Professor Halpern discovered a substance that showed itself to be experimentally interesting and was later to be used successfully in treating man: this substance was antergan. It was the point of departure for a series of researches that have not only brought us precious drugs, but have made possible a better understanding of the mechanism of allergic affections.

In 1946, Professor Halpern discovered the antihistaminic properties of derivatives of phenothiazine, the most active of which is phenergan. Experimentally, the antihistamines have shown themselves to be remarkable antagonists of histamine. As an example, the antihistamines also give complete protection against anaphylactic shock in animals and man. These properties are responsible for the unique characteristics of the synthetic antihistamines (fig. 6).

Clinically, the results vary according to the nature of the disease. The antihistamines, together with adrenalin, constitute the classic treatment for anaphylactic shock. They are consistently effective in hay fever, urticaria, Quincke's oedema, and certain eczemas; in asthma the results are less constant. Their toxicity is very low and as they have no major drawbacks, even when they are given for a long time, they can be regarded as the specific symptomatic treatment for allergic affections.

How do the antihistamines act? It has been shown experimentally that in their chemical structure these substances have affinities for the same cell structures as histamine has. There is antagonistic competition for the specific receptors between the poison and its antidote (fig. 6). Synthetic antihistamines have shown interesting properties in other fields which extend far beyond allergy.

## *Specific desensitization*

In contrast with the treatments already outlined, which are based on the neutralization of a histaminic substance liberated in the course of an antigen-antibody reaction, specific desensitization seeks to interfere with immunological reactions properly so called. Specific desensitization is applied only to hypersensitivity symptoms dependent on humoral allergy. Specific desensitization is practicable only when the antigen responsible for the hypersensitivity can be identified.

The antigen can be determined in two ways: either by exposing the allergic person to a substance to which he is supposed to be hypersensitive, or by making skin tests. For obvious reasons, the first technique has restricted possibilities. The advance of anti-allergic therapy by specific desensitization has been possible only since systematic skin tests have been practised. These consist in applying a small quantity of the suspected substance to the skin, after it has been scarified, or by injecting it under the skin. When the reaction is positive, it expresses itself by the appearance of an oedematous papule, surrounded by a red halo resembling the sting of a nettle at the place where the allergen has been introduced. This reaction appears fifteen to twenty minutes after the inoculation of the allergen.

In cases of dermal hypersensitivity by contact with a natural or synthetic chemical substance, the tests consist of the application of the substance on the intact or scarified skin.

Though they are apparently simple, skin tests have their limitations as well as their possibilities of error. They are positive only with certain substances—dust, pollens, hair, and food proteins of animal or vegetable origin. Only rarely are they positive in the case of chemical products and medicaments. Even when they are positive, skin tests should be compared with the clinical picture.

The identification of an allergenic substance by means of skin tests is of great diagnostic importance. In most cases, it justifies treatment by specific desensitization. This treatment consists in giving a hypodermic injection every two or three days, increasing the quantity of the antigenic substance progressively. By this means it is usually possible to establish tolerance of relatively important doses without incident. If, for instance, pollen solution is used, the progressive concentrations of the solutions will be 1/100,000, 1/10,000, 1/1,000, 1/100. With most patients one begins with a solution of 1/100,000 and progressively increases it till the concentration reaches 1/100.

The choice of the doses and the rate at which they are increased will depend on the tolerance of the patient. This is why treatment can only be given individually and must be given only by a specialist. The smallest overdose is capable of producing dramatic and dangerous reactions.

When the treatment is well carried out, it gives in most cases results that are equivalent to a cure. In many others, it is the only means by which the patient can carry on with his job.

How does desensitization work? The exact mechanism by which it suppresses or lessens the symptoms of hypersensitivity has not yet been completely elucidated. What has been proved is the appearance in the tissue fluids of an antibody of conventional type, which is a gammaglobulin. These antibodies, which are called 'blocking agents', neutralize the antigen before it combines with the sensitizing antibodies fixed on the cells.

Whether this explanation is valid or not, immunologically speaking, it is certain that alleviation of the symptoms of hypersensitivity is connected with the appearance of this type of antibody.

On the other hand, blocking antibodies mixed *in vitro* with the antigen neutralize its effect on the sensitized person in direct proportion to the antibodies' concentration.

Specific de-sensitization is certainly the most rational and most effective treatment for allergic affections caused by most of the respiratory allergens.

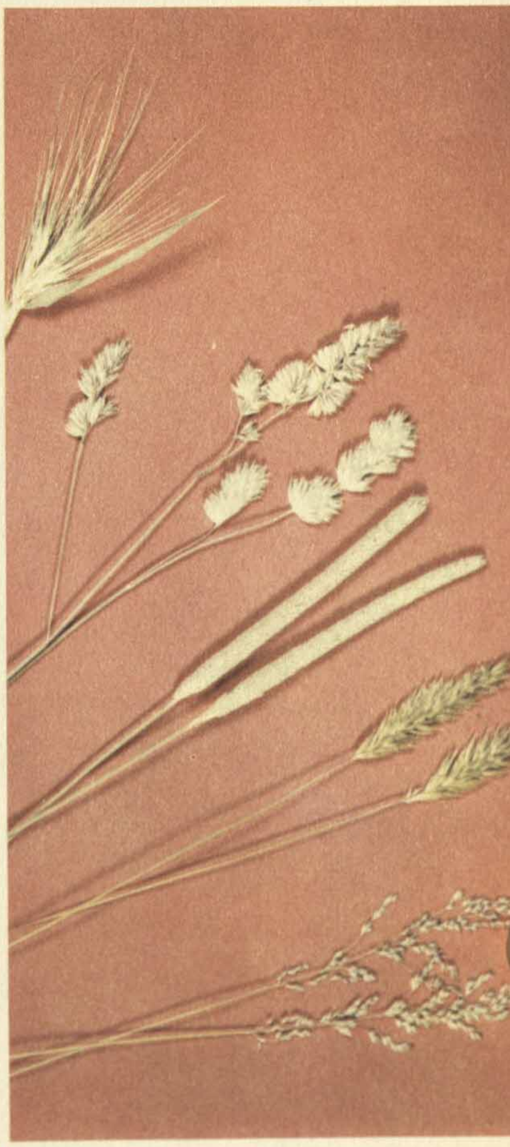
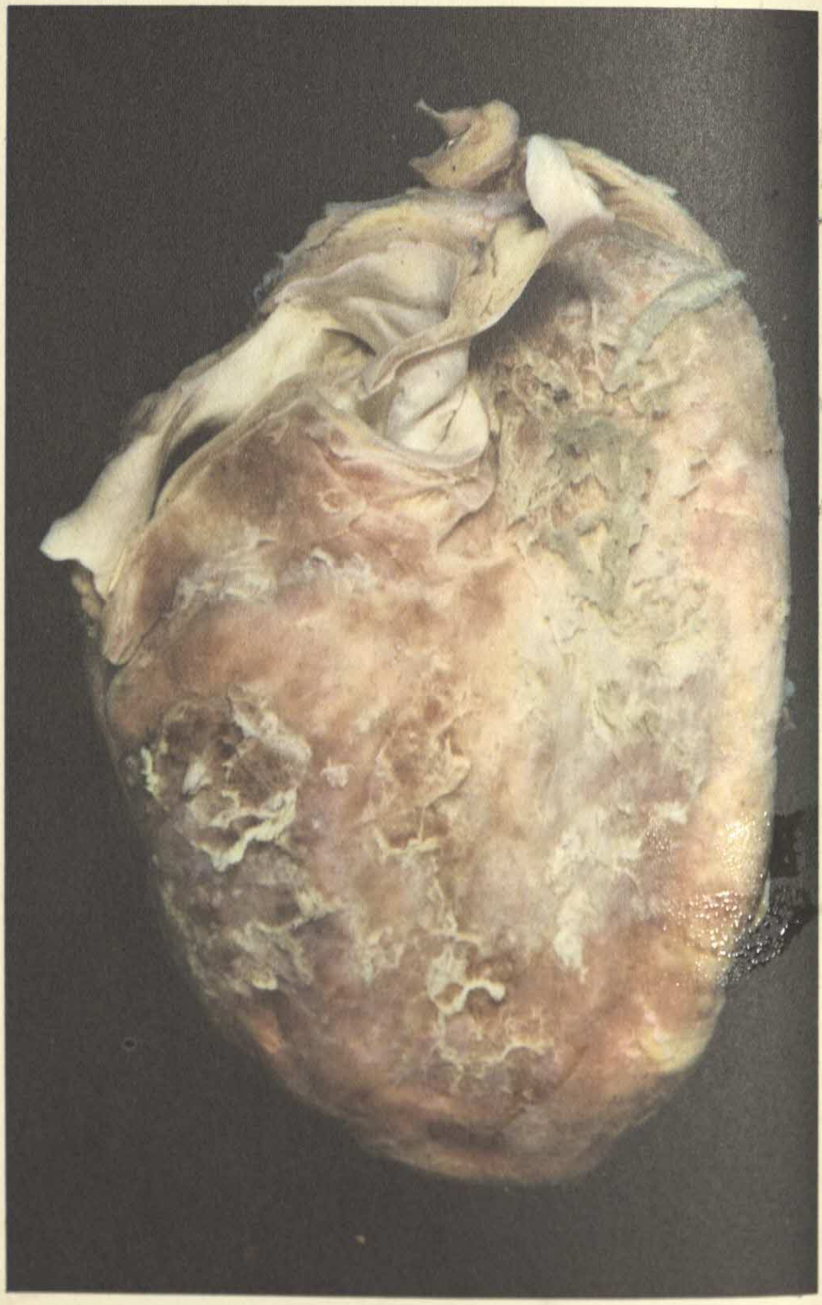
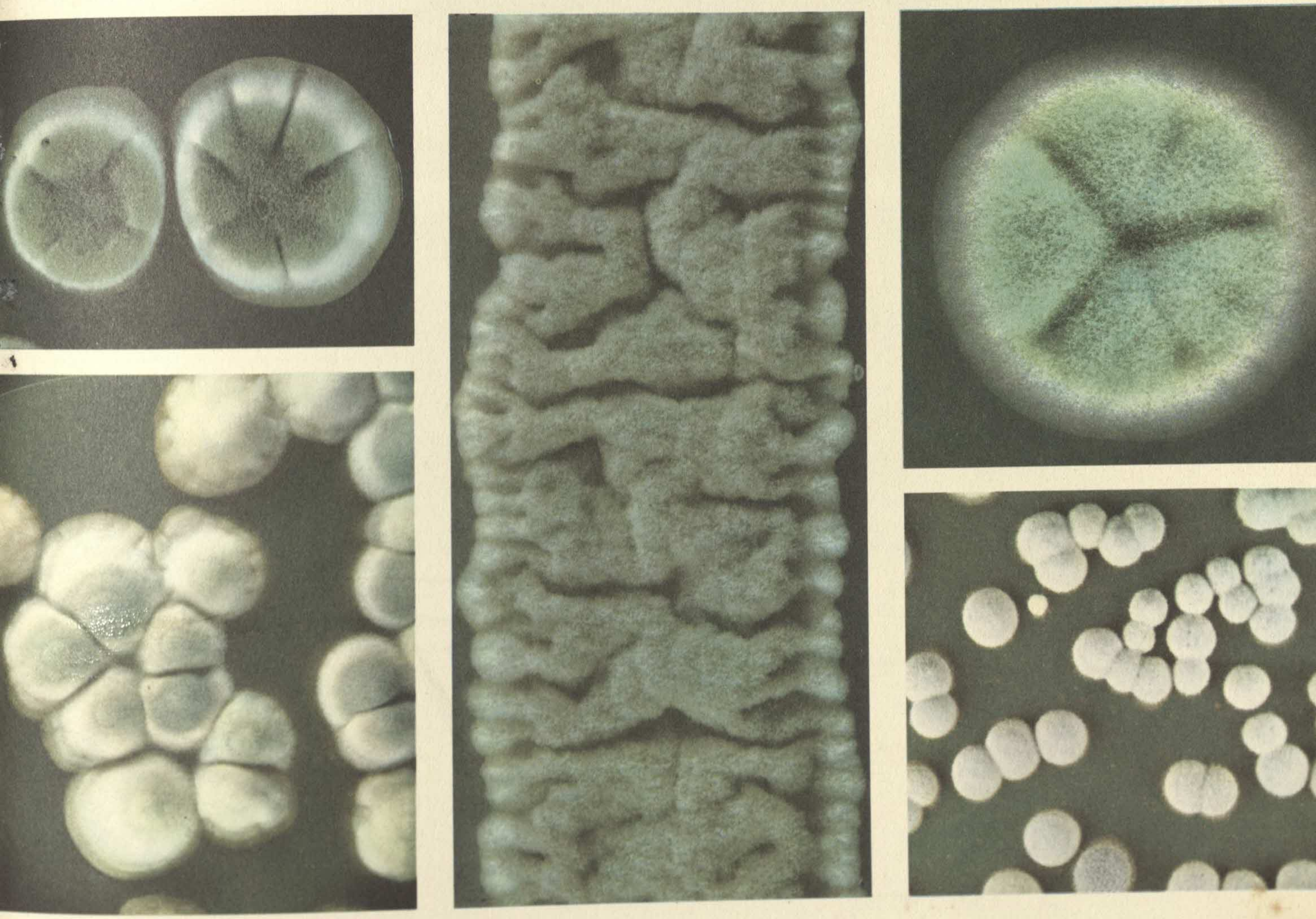


*Fig. 7. Different types of graminaceous plants whose pollen causes hay fever. From above downwards:* Poa pratensis, Autoxanthum novantum, Phleum pratense, Dactylus glomerata, Hordeum murinum.



*Nowadays doctors possess such marvellous resources that they have abandoned the old saying, 'Leave it to Nature'. But the substances which they administer must be prescribed accurately so as to ensure that the body's normal functions continue to operate and that its equilibrium is properly re-established. No therapeutic medicines, whether given intravenously* (left), *or parenterally, or by the mouth, should be*

# *Treatment of diseases*



*given without a careful estimate of their effects on the whole bodily system. This is just as true of time-honoured chemical preparations as of hormonal extracts. (corticoids) and (antibiotics (*above: *cultures of* Penicillium chrysogenum). *Antibiotics have caused a revolution in modern treatment; they are able to cure not only present-day microbial attacks, but also infections that used always to be fatal, such as malignant endocarditis* (left centre). *(Photo Lod; on the left, taken at the Institut Pasteur, Garches; in the centre, at the Hôpital St Antoine; those on the right, at the Société Industrielle pour la Fabrication des Antibiotiques, Paris).*

# The struggle against the vectors of infectious diseases

## *Henri GALLIARD*

*The idea that infectious diseases caused by micro-organisms, viruses, or parasitic animals could be conveyed by vectors is relatively recent. It is strange to think that for a long time the possibility that biting and blood-sucking arthropods, fleas, bugs, mosquitoes and ticks, might inoculate germs had never been considered. Water, soil or miasmas were believed to be responsible for infections. From 1893 onwards, however, the part played by parasites in propagating various diseases, especially malaria and sleeping sickness, has become more and more evident.*(1)

From time immemorial malaria has been of major concern in the lives of people all over the world. Before contact-insecticides came into use the only protection against it was preventive chemotherapy and campaigns, carried out with petroleum and Paris Green, against the larvae of its mosquito vectors—apart from mechanical measures such as drainage, dredging, and the filling up of swampy areas.

Suddenly, it was realized, about 1938, that a chlorinated product, DDT (known since 1874) has a lethal effect on certain insects that are parasitic on plants. Consequently, the idea arose of using it against adult mosquitoes and their larvae. The results were immediate and surprising, especially in Italy and Greece. DDT, unlike any other insecticide, has a persistant or remanent effect lasting for weeks or even months. In addition, it became possible for public health authorities to destroy adult mosquitoes by spraying houses with DDT, which could be done without even having to ask the public to co-operate. This was indeed a revolution. In certain countries the effects were shown by a sudden cessation of infectious diseases and a considerable reduction in their mortality rate.

Later on, other products were brought into use: the gamma isomer of benzene hexachloride, or HCH, or gammexane—more toxic than DDT, but with a shorter remanent effect—and dieldrin, which seems to fulfil the optimum conditions of toxicity and remanent effect. Besides these, there are numerous other products, notably the organophosphorus compounds, which are extremely active but dangerous to use.(2)

Malaria, however, in spite of the astonishing results obtained by the use of contact-insecticides, continues to preoccupy the experts. It was clear from the first few years of their use that the effects of these insecticides vary in different regions. These variations are due to the particular biology of the local species of the anopheline mosquito vectors. Certain species are not very pathogenic because they prefer to attack animals. Others, which attack man, bite out of doors and consequently are not affected by insecticides applied to the walls of huts or houses. The domestic species, which bite indoors and rest inside buildings, poison themselves by contact with surfaces treated with DDT.

In Africa, the formidable species *Anopheles gambiae* lives in close contact with man and attacks him ferociously. But DDT does not kill this species, it merely has an irritant effect; by preventing the mosquito from settling, it protects it from being poisoned. The mosquito takes refuge in the open, but this does not by any means stop it from gorging itself on man and infecting him, or infecting itself from him afresh, and when this happens the suppression of malaria is difficult.

The ability of certain mosquitoes, because of their peculiar biological constitution, to remain immune to the effects of insecticides is called 'behavioural resistance'. There is also a physiological resistance. A serious problem arose when in 1947 it was found that flies, lice, fleas and bugs were becoming increasingly resistant to insecticides. The question was how would *Anopheles* behave? Innumerable experiments were made to solve this problem.

(1) *See the chapter on Parasitism and Symbiosis by Jean G. Baer, in Volume 2 of* The Living Universe. *See also, at the end of this chapter, the historical notes on the discoveries relating to vectors of micro-organisms.*

(2) *See the chapter on Chemical War on Insects by Paul Pesson, in Volume 2 of* The Living Universe.

The mechanism of resistance is complex. So far as *Anopheles* are concerned, the problem is a genetic one. There are thirty-one species, or varieties of species, of *Anopheles* which are resistant to either DDT or dieldrin or to gammexane (HCH). Generally speaking, the anophelines that are resistant to DDT are susceptible to dieldrin and gammexane, and *vice versa*. But resistance does not mean that there have not been some remarkable results. In Greece, for example, the success achieved since 1939 by spraying has not been affected either by its being virtually discontinued or by resistance to insecticides appearing in the vectors.

There have been interesting results in Africa. In spite of the resistance of *Anopheles gambiae* to the dieldrin HCH group, malaria has been considerably reduced over a period of two years, thanks to the use of DDT, so that one can say it has been virtually eradicated from certain areas. Thanks to insecticides, and in spite of uneven results, malaria is in many regions no longer endemic but is confined to limited areas. Although resistance is occasionally observed, the stopping of transmission has been so effective that no disquieting recurrence of clinical cases has taken place, even in regions where spraying has been discontinued.

The idea of trying to eliminate the anophelines completely has been abandoned as being impossible. Instead the foci in which malaria reappears are attacked by treating the patients and carriers of the parasites (this, of course, is *malaria control*, not *mosquito control*). Spraying with insecticides is only done again when there is a fresh outbreak of clinical cases. Then, every means of stamping out the focus must be used, just as it would be in the case of an epidemic disease.

Nowadays, infected persons can be treated with the certainty that they will not be immediately reinfected. The plan agreed on by the World Health Organization and adopted by numerous countries for the extinction of the parasites in man by chemotherapy, means that more than 1,200 millions are now protected from malaria.

## *Other infections transmitted by culicid flies*

Apart from malaria, numerous other infections are transmitted by Culicidae other than anophelines. Against these, too, contact-insecticides have shown themselves to be effective, though to a lesser degree. The mosquito, *Culex fatigans*, for instance, a domestic species distributed throughout the tropical zone and important as the vector of Bancroftian filariasis[3] is resistant to DDT. But *Aedes (Stegomyia) aegypti*, which transmits dengue and urban yellow fever, has been practically wiped out. So have the mosquito vectors of the viruses that cause encephalitis, where it has been possible to attack them, although there are some instances of resistance.

Other susceptible insect vectors have been easily suppressed. They include the sandfly *(Phlebotomus)* vector of Leishmaniasis,[4] but the biology of these flies is variable, and, as with anopheline mosquitoes, there is a variety of species and biotypes. These are active in the transmission of diseases, but they are also more vulnerable, while the wild *Phlebotomus* escapes insecticidal measures.

Among other insects, lice, which transmit the recurrent fevers and cosmopolitan epidemic typhus,[5] and fleas, which are vectors of bubonic plague, are also susceptible to insecticides, although resistant strains, or strains that have become resistant, have been detected among these insects.

## *Sleeping sickness*

The destruction of flies of the African genus *Glossina*, which are vectors of sleeping sickness, has long been attempted, with varying results. Agronomic measures, such as the clearing away of scrub and selective clearing of trees have been tried with a view to affecting the ecology of *Glossina*. It has even been suggested that wild game should be destroyed and in certain areas this has been done. By means of these measures it has been possible to make some areas healthy. Evidently, DDT, dieldrin and benzene hexachloride give better results, but the permanence of the effects of these chemicals is slight when they are applied to vegetation. In some areas the pelts of certain mammals, on which various species of tsetse flies feed, have also been sprayed with insecticides.

## *Infections transmitted by acarines*

Acarina play an important part in the transmission of certain infections, especially the epidemic fevers, such as tick typhus (Rocky Mountain spotted fever or Blue Disease), tick-bite fever, and scrub typhus or Japanese river fever. Amongst the Ixodidae or ticks, Ornithodorus transmits a recurrent

Triatoma pallidipennis, *a Mexican bug, vector of Chagas' disease; here the insect is shown with the wings unfolded. (Photo Lod). Darwin was probably infected with Chagas' disease by the South American species of this insect.*

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(3) Bancroft's filariasis *is transmitted by mosquitoes; the mechanism of this transmission was discovered by Patrick Manson, and also later by C. Low, between 1878 and 1900. A filarial worm,* Onchocerca, *responsible for the blindness of hundreds of thousands of Africans, is transmitted by simulids or biting midges.*

(4) Leishmania, *flagellate protozoa living in the blood, the cause of cutaneous leishmaniasis and kala-azar, have as their vectors sandflies (Phlebotominae), which are small blood-sucking Diptera.*

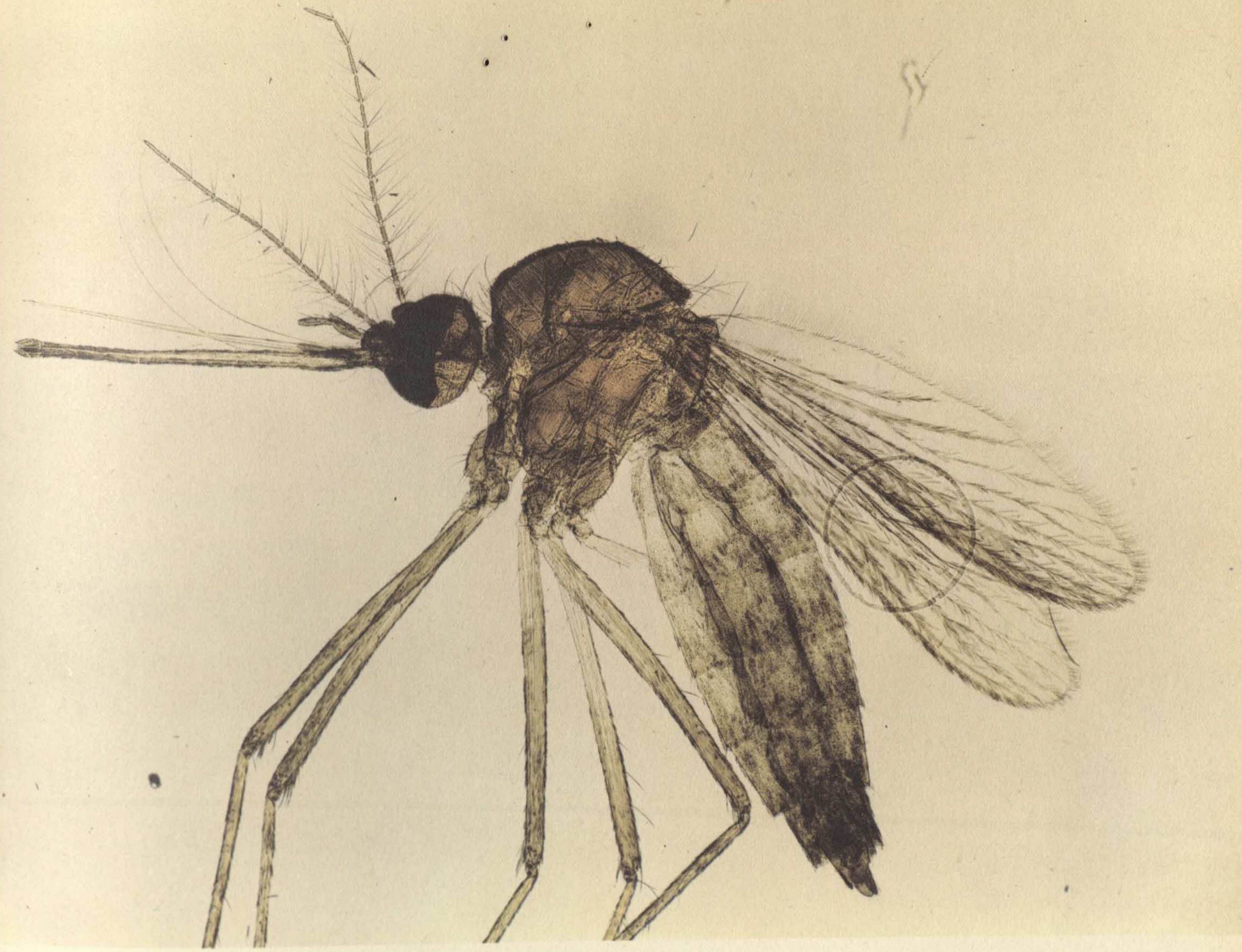
*These two photographs were taken in the Indian State of Travancore. This is a swampy region, favourable to the development of mosquito larvae. On the left, a pool for soaking coconuts, the fibre of which is used for making a form of textile. The water must be cleared of vegetation in order to destroy the larvae. On the right, another place where mosquito larvae are likely to be found: a canal between a lagoon and the sea. The destruction of vectors of tropical diseases caused by parasites has a notable effect in reducing their incidence (in this case, filariasis). (Illustration by courtesy of Professor Galliard).*

*a*

*c*

*d*

*b*



e

## *Some vectors of micro-organisms*

*The vectors of infectious diseases can be carried by a number of organisms, some of which are shown on these pages:*

- *(a)* Triatoma pallidipennis *(normal attitude).*
- *(b)* Triatoma vitticeps *(Brazil); vector of Chagas' disease* (Trypanosoma cruzi).
- *(c)* Ornithodorus, *the vector of recurrent fever caused by* Borrelia duttoni.
- *(d)* Limnaea truncatula, *intermediate host of* Fasciola hepatica *(liver fluke).*
- *(e)* Culex fatigans *female, vector of lymphatic filariasis caused by* Wuchereria bancrofti.

fever to man (relapsing fever), called 'tick fever'. The ticks which live on animals are economically important because they transmit to cattle fatal infections caused by parasites of the red blood cells, such as *Piroplasma* and *Theileria*. Arsenic, formerly used as an insecticide in such cases, has given place to DDT, BHC and dieldrin. But some strains of ticks are resistant to these insecticides, and some to arsenic, just as anopheline mosquitoes are resistant to insecticides to which other species are susceptible. For example, there are ticks which, although resistant to both arsenic and BHC, are susceptible to DDT. It is often necessary to use chlorinated hydrocarbons, such as chlordane or chlorinated camphene, which are sometimes ineffective against ticks that are already resistant to BHC.

## *Bilharziasis or schistosomiasis*

Bilharziasis[6] has so far resisted most prophylactic measures, such as health education, improvements in sanitation and campaigns based on mass treatment. Antimony derivatives have some effect on clinical symptoms and reduce the number of eggs in the body, but it is a thankless task to treat patients who reinfect themselves through contact with water.

In the life cycle of the parasite the intermediate host is a snail which the worm embryo penetrates; from this snail emerges the infective larva or *cercaria*. The larva, which lives in the water, penetrates the skin and settles down in the venous system. There the worms, when they have reached sexual maturity, lay their eggs, which are usually passed out through the digestive tract or in the urine, according to the species of worm involved; but a considerable number of these eggs can be carried away to form emboli in one or other of the organs and this may cause serious organic lesions.

For a long time 'molluscicides' have been used to kill snails. The first one to be tried (it is still prescribed for the purpose) was copper sulphate, which is toxic to snails, but has little effect on mammals or on fish, but it does not kill the snails' eggs. Marked progress has been achieved by using the pentachlorophenates of sodium or copper. The former is cheap and simple to use. It is unnecessary to destroy herbage before using it, as must be done when copper sulphate is used. It can be discharged into irrigation canals and will kill the snails a long way away from the place where it is put into the water. It also has the advantage of being able to kill the snails' eggs and the infective cercariae. Its drawback is that it decomposes in sunlight. In addition, it is also very toxic to fish, and it has an irritant effect on the snails which may lead them to leave their habitat. In spite of the irritation which it causes to the mucosa, in the recommended concentrations, it is not toxic to man or to domesticated animals and has no corrosive action on materials. Pentachlorophenate of copper is also very effective and the results last longer than those of the sodium salt or copper sulphate.

In some parts of Africa a new molluscicide, Bayer 73, has been used which is active in concentrations much lower than those of other molluscicides. It is toxic to the molluscs and their eggs and also to the cercariae, and, like copper sulphate, is virtually harmless to man and cattle, being neither irritant or corrosive.

Aqualin, a herbicide used to destroy submerged aquatic vegetation, has acrolein as its active ingredient. It is highly toxic to snails and their eggs and must be handled with caution. Another molluscicide, ICI 24 223, has recently been tested; in the concentrations used to kill snails it is toxic to fish, but not to man.

Knowledge of the vectors of micro-organisms is now sufficiently extensive to allow effective campaigns to be waged against them. Thus, we know that any one arthropod or snail will not indiscriminately permit the development of any kind of parasite or virus.

There is a strictly *specific* adaptation of one species of parasite to one species of intermediate host. This specificity means, for example, that the geographical distribution of sleeping sickness corresponds to that of *Glossina* (tsetse flies). Similarly, that of bilharziasis is determined by the geographical distribution of the various snails which carry cercariae. On the other hand, Bancroftian filariasis and malaria, which are transmitted by mosquitoes, have a world-wide distribution limited only by suitable climatic conditions.

It is clear that the effects of the campaign against bilharziasis by means of molluscicides cannot be compared to those of the campaign against malaria, in which contact-insecticides have been decisive. Until an ideal molluscicide is discovered, bilharziasis will therefore remain a disease against which exhaustive campaigns cannot profitably be waged—except in extremely limited areas—because of the impossibility of preventing human contact with water, in which cercariae live.

### HISTORICAL NOTES

1877–80
Patrick MANSON *studied the transmission of Bancroft's filaria by mosquitoes.* SMITH *and* KILBORNE *discovered that the bites of ticks give Texas fever to cattle: this led to the conception of a 'vector of micro-organisms'.*

1898
Ronald ROSS *(and later* GRASSI, BASTIANELLI *and* BIGNAMI) *discovered the method by which mosquitoes transmit malaria.*

1900
C. LOW *discovered the precise transmission mechanism of Bancroft's filaria. Thus the idea of 'intermediate host' was substituted for that of 'vector'; inside the intermediate host, the pathogenic agents taken from man undergo a 'life cycle' resulting in an infective stage or 'metacyclic form'.*

1909
KLEINE, *and then* BRUCE, *discovered the method by which sleeping sickness is transmitted by* Glossina.
CHAGAS, *in Brazil, showed that* Trypanosoma cruzi *is transmitted to man by the bite of Triatoma, a blood-sucking hemipterous insect.*

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(5) *The* Rickettsias *of exanthematic typhus are transmitted by lice and ticks. There are mosquitoes which transmit virus diseases such as yellow fever, dengue and other encephalitic viruses, and fleas which transmit plague.*

(6) *The schistosomes of* Bilharzia *use fresh-water molluscs as their intermediate hosts, as do liver flukes.*

# Vaccines and sera

*Albert DELAUNAY*

*The first empirical attempts at vaccination date back nearly a thousand years. Today it is one of the elementary preventive and prophylactic measures that exist in many countries. Vaccines, which are made either from killed or attenuated living bacteria or viruses, give protection against infective disease. There is often a tendency to confuse vaccination with serum treatment, although these are fundamentally different.*

The word vaccine is used for a preparation which, when it is injected into a person or an animal, produces a state of *active* immunity; that is, it incites the organism to produce immunity. The immunity thus produced will be a *specific* one, which means that the person who has been treated will be protected only against the micro-organism or the toxin contained in the vaccine.

The history of vaccination goes back to the first attempts that were made against smallpox. In the twelfth century, both the Chinese and the Siamese, when they wanted to protect anyone from smallpox, took crusts from people suffering from the disease and put them up the noses of those whom they wished to safeguard. Empiricism had shown them that persons treated in this way were often spared during epidemics. Early in the eighteenth century, Lady Mary Wortley Montague, the distinguished wife of the British ambassador at Constantinople, made this known when she returned to England. Here the method was also tried successfully, though it was not entirely without danger. If the crusts that were put into the nostrils were too virulent, the disease that this treatment sought to avoid was started. So enquiring minds set out to seek another method. Success smiled on Jenner, an English doctor who had been impressed by the rarity of smallpox among people who had suffered from a benign infection of cattle, known as *cowpox* or vaccinia. One day Jenner decided to inoculate a young boy with vaccinia. The experiment caused no harm and a few days later he inoculated the same boy with smallpox; but in contrast to what would have happened in other circumstances, the disease did not appear. Evidently, Jenner thought, all was well because the 'vaccination' produced a state of immunity: Jennerian vaccination had been discovered. This was at the end of the eighteenth century. After nearly two centuries, there is still good reason to admire Jenner's idea, even though he had the benefit of an exceptionally favourable case. It is only very rarely that one can be vaccinated against a disease by using a micro-organism different from that which causes the disease itself.

Jennerian vaccination, though it had been severely criticized (usually by ignorant people) eventually succeeded in becoming established. It haunted the mind of Pasteur from the beginning of his research on microbes. He wanted to do for other infections what

*Fig. 1. Vaccines injected into animals are sometimes composed of a suspension of bacteria which resemble the microbe shown in this illustration,* Proteus vulgaris. *(Photo Lod).*

Jenner had succeeded in doing for smallpox, and ultimately his dream became a reality. In this fact lies the whole history of the discovery of preventive methods against chicken cholera, anthrax, and finally rabies (1885). In homage to the English doctor, Pasteur decided to give this method the name of *vaccination.*

Since Pasteur's day, numerous other vaccines have been discovered. A vaccine may be composed of living or dead organisms suspended in water, or even their toxins in solution.

## *Living bacteria vaccines*

The best known of these is the tuberculosis vaccine of Calmette-Guérin, called B.C.G. vaccine. Its discovery was the culmination of prolonged and painstaking research, and it was introduced in 1923.

The *Mycobacterium tuberculosis* bacillus present in the vaccine is a strain of bovine origin which has been subjected to repeated cultures on a nutritive medium to which bile has been added. That it can immunize animals is indisputable. Thus when cattle free from spontaneous tuberculosis are treated with B.C.G., they almost always resist intravenous inoculation of a dose of virulent bacilli which in unvaccinated healthy control cattle would be sufficient to cause fatal generalized tuberculosis within a few weeks. This resistance to re-infection is roughly comparable to that of an animal which has a benign or latent infection.

Tuberculosis in man is generally caused by a bacillus of the human type, but because the bovine and human types are closely related to each other, phenomena of cross-immunity often occur, so the use of B.C.G. vaccine for vaccination is justified.

By Calmette's original method, B.C.G. was given orally from the first few days of life. This early administration had a double aim: to immunize newborn babies before they could be infected by virulent air-borne bacilli or by food, and to profit from the fact that the permeability of the intestine to the living bacilli in the vaccine seemed to be especially high at birth. Millions of babies have been treated by this method. What are the results?

First, it must be emphasized that the vaccine is harmless; the non-virulence of the Calmette-Guérin attenuated bacillus remains perfectly stable. A few years ago, great concern arose because of the use of poor quality vaccine in certain mass campaigns. Innumerable statistics published in various countries indicate the efficacy of the vaccine when it is given orally. Nevertheless, the tuberculin skin test is often negative after this method of administration; in other words, it is impossible to show the existence of allergic sensitivity. However, it seems that this is required for producing good resistance to the disease. To facilitate the appearance of this allergic condition, various methods have been proposed. The more recent of these, devised since 1940, have been completely successful. They show the importance of using a vaccine rich in bacilli, and that parenteral administration is preferable to oral administration. It is best to introduce B.C.G. by slight multiple punctures of the skin (Rosenthal), or by depositing it on a scarification of the skin (Nègre and Bretey; Weill-Hallé). This method sometimes causes local lesions, but these are always slight and such discomfort as they may cause is compensated for by a high degree of protection.

Vaccination by parenteral routes is adopted for all newborn infants (up to the fifteenth day of life), and for older children, adolescents, and adults who have not given rise to any suspicion of tuberculosis but who are insensitive to tuberculin. After vaccination, tuberculin tests at intervals of one or several years are strongly advisable; those who have lost their sensitivity should be re-vaccinated. It begins to look as though the long-awaited solution to the problem of preventing tuberculosis has been found.

Other methods besides that of Calmette and Guérin involve the use of living and attenuated bacteria. In Madagascar, Girard and Robic, in their successful campaign against plague, used a vaccine made of bacilli of very much attenuated virulence.

## *Killed bacteria vaccines*

The first data on this subject resulted from the work of Roux and Chamberland, and from that of Salmon and Smith. Some years later, in 1888, Chantemesse and Widal succeeded in vaccinating laboratory animals against typhoid fever, using heat-killed bacteria. In 1898, the first anti-typhoid vaccinations were made on man by Wright in England and by Pfeiffer and Kolle in Germany. The First World War brought about the spread of their method. Today, typhoid vaccine (a mixture of typhoid and paratyphoid bacteria) is widely used. It is usually made of a suspension of the bodies of bacteria killed either by heat (55–60°C) or by formol, phenol, alcohol, or ether (H. Vincent), iodine, etc. The bacteria to be used must not have undergone any antigenic weakening and must contain a full amount of body antigens. The vaccination entails at least three subcutaneous injections, which are made at intervals of a few weeks, and involve a total of some thousands of millions of bacteria. Each injection is accompanied by a reaction (aching and fever), but this does not usually last long. Under no circumstances should the vaccine be administered orally.

The results of typhoid-paratyphoid vaccination during and after the two World Wars testify to its complete success and justify its use. Nevertheless, it does not give an absolute guarantee against infection. It only diminishes disease and mortality in many cases.

There is also a killed vaccine for cholera which has been frequently used. It is a long time since use was made of Ferran's and Haffkine's live vaccine. Vaccination against cholera is used successfully every day in Asia and particularly in India, where the disease is prevalent.

Another killed vaccine is used against whooping cough, a children's disease which often leaves disquieting after-effects. It is caused by a small bacillus discovered by Bordet and Gengou.

## *Toxoids*

The poisons secreted by certain bacteria, known as exotoxins, generally have marked vaccinating power. Unfortunately, they cannot be used just as they are because of their toxic effects. Various methods of counteracting these effects have been tried; it has been suggested, for instance, that these particular bacteria should be injected, together with the appropriate dose of the corresponding antitoxin (Park). Some successes have been recorded, but more failures, including some fatalities, have occurred. Attempts have also been made to use exotoxins that have been treated with an antiseptic such as iodine, hypochlorite, or formol. But the method of their preparation was badly controlled and did not inspire confidence.

The distinction of having found out how to transform bacterial exotoxins, which are very formidable substances, into beneficent vaccines belongs to the British scientists, Glenny, Allen, and Hopkins.

Since 1923, the combined effect of heat and formol has been used to deprive exotoxins of their toxic powers. The formolized toxins (at $5^{\circ}/_{\circ\circ}$) are kept for a month at 40°C. After this, though they are no longer completely toxic, they remain very strongly antigenic and compel organisms which receive them to manufacture large amounts of antibodies which are as valuable as the antitoxins themselves. These modified toxins are called toxoids. Many have been made, the two most important being those used for vaccination against diphtheria and tetanus.

Diphtheria vaccination is extensively used and in some countries it has been made compulsory. It is especially important for children, adolescents, and young adults. It consists of three subcutaneous injections of diphtheria toxoid with an interval of two weeks between each injection. In order to reinforce the resulting immunity, a booster dose is given a year later. The strength of the immunization can be verified by the Schick test. This reaction, which appears on the skin, is positive in those in whose body fluids there is practically no diphtheria antitoxin. On the other hand, it is negative—with some exceptions—in all those who have been properly vaccinated with the specific toxoid.

The efficacy of diphtheria vaccination has been established by innumerable records. Tens of millions of people in different countries have benefited from it. The results show conclusively that diphtheria is infinitely rarer and, when it does occur, less serious in those who have been vaccinated than in those who have not. In New York, for example, where vaccinations were done on a large scale, the annual number of deaths from diphtheria in

*Fig. 2. Tetanus serum made it possible to save many lives during the Second World War. (Photo Lod).*

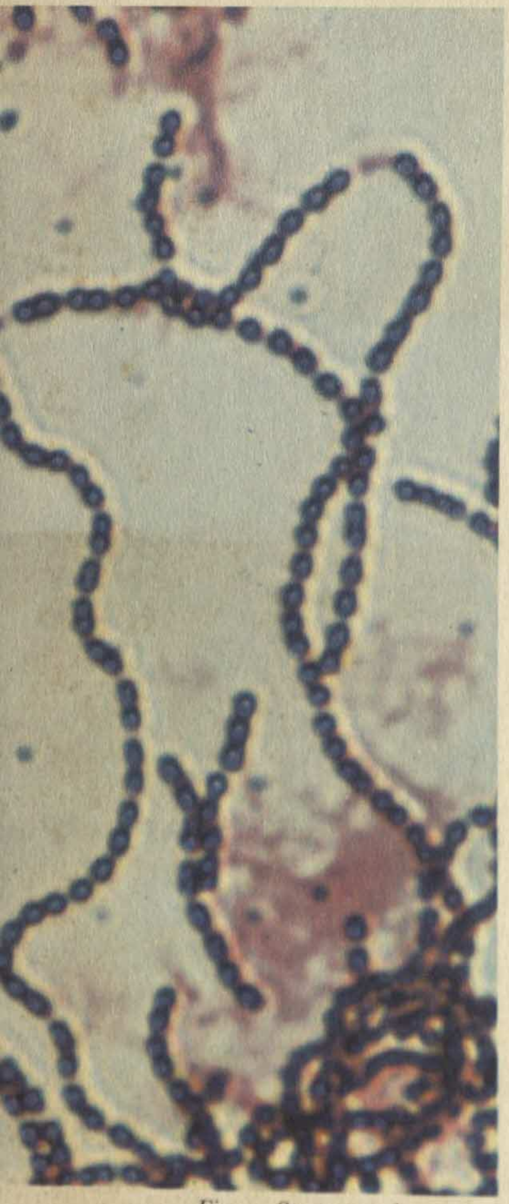

*Fig. 3. Streptococcal serum was one of the first therapeutic sera to be prepared: streptococcus culture showing bacteria disposed in chains. (Photo Lod).*

1924 was seven hundred; in 1936 it was only thirty-five.

Tetanus vaccination is done in exactly the same way as diphtheria vaccination; in fact, it is often recommended, especially for children and members of the armed services, that the two should be done together. There is no doubt at all of its value, which is proved by the following facts: all the American troops who fought in the Normandy campaign in 1944, and most of the British, had been vaccinated against tetanus, with which the soil of the battle area was highly impregnated. Not so the Germans, however, of whom quite a number had not been vaccinated. Those of the Allied wounded who had also not been vaccinated were given tetanus injections on the battlefield; and those who had already been vaccinated were given a dose of toxoid. Not one single case of tetanus occurred. But among the non-vaccinated Germans there were numerous cases, some of them fatal.

Viral vaccines are composed of preparations which, depending on the virus used, may be made up either of living virus particles the virulence of which has been attenuated (Jennerian vaccination, vaccine against yellow fever, smallpox vaccine, certain vaccines used against poliolyelitis) or killed viruses, eg, rabies or foot-and-mouth vaccines. All these are generally admitted to be efficacious.

## Serum treatment

How do vaccines act? How can they confer immunity? Almost always, vaccines appear to do this by stimulating the formation of antibodies through the antigens which they bring to the body.[1]

The antitoxins in vaccinated persons neutralize the exotoxins secreted by a corresponding multiplying bacterium that has entered the tissues. The antibodies come to the aid of the phagocytes and finally prevent the bacterium from entering cells susceptible to them.

Immunity produced by vaccination has the advantage of being long-lasting, but the disadvantage of being slow to act. But in some cases, for example, where infection already exists, it is desirable to enrich the body as quickly as possible with a substantial dose of antibody. This can be done by serum treatment.

This consists of injecting the serum of an animal rich in antibodies. The animal most often used is a horse, which itself will have been immunized, either by bacteria (living or killed) or by toxoids. Either the natural serum can be used or purified serum; that is, serum from which most inactive proteins have been removed.

Since serum treatment was first developed by Roux more than half a century ago, it has been extraordinarily successful and there is every indication of its being so in the case of diphtheria and tetanus. But since the discovery of sulphonamides and antibiotics, antibacterial serum treatment (against, for example, pneumococci, meningococci, and streptococci) has lost much of its importance.

The injection of a serum gives a *passive* immunity which appears immediately but is transitory because the antibodies, which are foreign proteins, are soon eliminated in the urine. Once the antibodies have disappeared, the organism recovers all its susceptibility to infection. But it does not revert completely to its original condition. It has, in fact, manufactured antibodies against the proteins introduced in the therapeutic serum and these, by a mechanism not yet fully explained, predispose it to anaphylactic sensitivity.

Some years before the Second World War, Ramon suggested that a combined treatment should be given for diphtheria and tetanus, consisting of a simultaneous injection of toxoid and serum given in different places; this is known as *serum-toxoid therapy*. It has the advantage that the immediate, though transient, passive immunity given by the serum is followed by an active immunity conferred by the toxoid, which gives protection against the possibility of a recurrence or a relapse.

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(1) *See the chapter on 'Antibodies' by Robert Fasquelle in Volume 4 of* The Living Universe.

# Antibiotics

*Ernst B. CHAIN*

*It has been known since the time when micro-organisms could be grown in culture, ie, since the days of Pasteur, that certain species of micro-organisms inhibit the growth of others. In most instances this phenomenon, known as microbial antagonism, is due to the production by the antagonistic species of metabolites endowed with antimicrobial activity. Such substances are now known under the name of antibiotics.*

The first use of an antibiotic in therapeutic medicine for the treatment of systemic bacterial infections dates back to 1940, when Florey, Chain, and their colleagues reported that penicillin, an antibacterial metabolite produced by a species of *Penicillium* described eleven years earlier by A. Fleming, had remarkable curative power, both in experimental infections in mice with several important pathogens, including staphylococcus, streptococcus and spore-forming anaerobes, as well as in some very severe clinical bacterial infections.

These observations mark the beginning of a new epoch in clinical medicine, the era of antibiotics for the treatment of bacterial infections. Following the description of the extraordinary chemotherapeutic properties of penicillin, a very intensive world-wide search for other antibiotics was begun which has brought to light many hundreds of new antibacterial substances of microbial origin. Though only a very small number of these has found practical application in medicine, their antibacterial range was so wide that it covered a large majority of the most dangerous bacterial infections in both man and animals, and, in consequence, most of them can now be brought under control.

The effort made to discover new antibiotics has been vast; many hundreds of thousands of micro-organisms have been screened, and the field has been exploited to such an extent that in the author's opinion it is very unlikely that the continuation of this kind of research will lead to the discovery of many new types of antimicrobial metabolites. For this reason, the time would seem opportune for a general stock-taking of the achievements in the whole field of antibiotics and a general appraisal of their impact on therapeutic medicine.

## Antibiotics of wide clinical use

Of the many hundreds of antibiotics discovered, only the following few have found

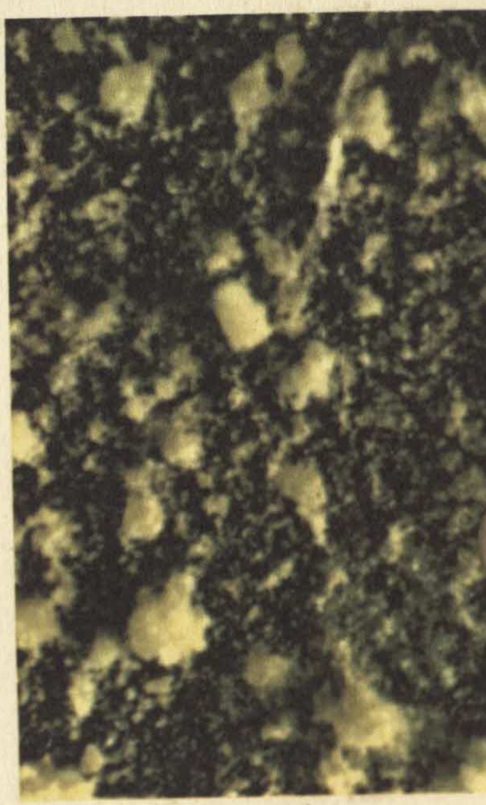


*Fig. 1. A wide-spectrum antibiotic: tetracyclin chlorhydrate. (Photo Lod, taken in the Specia Laboratories).*

*Fig. 2. The mould* Circinella umbellata *is the starting point for the preparation of certain antibiotics. (Photo Professor Guillemat, École nationale d'Agriculture, Grignon).*

wide application in medicine and are still extensively used in the treatment of systemic infections:

1 The penicillins
2 Streptomycin
3 Chloramphenicol
4 The tetracyclines

With the exception of the penicillins, all the other antibiotics of practical importance are metabolic products of soil actinomycetes.

## *The penicillins*

The penicillin molecule consists of a nucleus of dipeptide nature, named 6-amino penicillanic acid (fig. 3, *2*) and a side-chain acid linkage in peptide linkage to the free amino group of the nucleus. The two amino acids of which the nucleus is built up are β-thiovaline and formyl glycin, linked together in a characteristic fused thiazolidine-β-lactam ring system. This ring system, under the influence of the side chain, readily undergoes hydrolysis, followed by intramolecular rearrangements. These reactions, which occur in acid and alkaline media and under the influence of certain heavy metal ions, are the reason for the instability of the penicillin molecule, which has retarded the discovery of its chemotherapeutic power by a decade. We shall describe the case of benzylpenicillin, the most commonly used of the penicillins, in which the side chain is phenylacetic acid.

Destruction of benzylpenicillin by the opening of the β-lactam ring (reaction I→III) is brought about not only by alkali, but also by an enzyme, termed penicillinase, which is present in many bacteria. Naturally, bacteria producing this enzyme are resistant to the action of benzylpenicillin.

Benzylpenicillin is produced industrially by natural fermentation in fermenters varying in capacity between 30,000 and 300,000 litres. The mould is a selected strain of *Penicillium chrysogenum* which is grown in a culture medium consisting of some nitrogenous material such as corn-steep liquor, peanut or soya bean meal, and a sugar, such as lactose, glucose, or sucrose. Aeration is effected by blowing air through the mechanically agitated culture medium. The whole system must be kept rigorously sterile.

The side-chain acid of benzylpenicillin, phenylacetic acid, is added to the culture medium during the fermentation process and incorporated by the mould into the penicillin nucleus. Yields of 6 mg and above are readily obtained with good strains of *P. chrysogenum*, and benzylpenicillin has become a cheap drug.

Not only phenylacetic acid, but many other substituted acids can be incorporated into the penicillin nucleus by the mould, and in this way many new semi-synthetic penicillins with different substituted acetic acid side-chains have been obtained by fermentation. One of these, phenoxymethylpenicillin, is obtained by the addition of phenoxy acetic acid, $C_6H_5OCH_2 \cdot COOH$, to the culture medium. It is acid-stable and has therefore found widespread clinical use as an oral penicillin preparation; the common benzylpenicillin is acid-sensitive and must therefore be administered by injection.

While the mould will incorporate only derivatives of acetic acid into the penicillin nucleus, it is possible to obtain penicillins with a very large variety of other side-chain acids by direct acylation of the nucleus. The nucleus of the penicillin molecule, 6-aminopenicillanic acid, is readily obtained by enzymatic hydrolysis of the side-chain from benzylpenicillin by means of bacterial enzymes, termed penicillin amidases. Enzymatic hydrolysis of benzylpenicillin goes practically to completion and pure 6-aminopenicillanic acid can be obtained in yields of over 70 per cent. 6-aminopenicillanic acid can also be obtained by direct fermentation if no side-chain precursor acid is added, but its isolation and preparation in pure form from the culture medium is more difficult than by enzymatic splitting of benzylpenicillin.

Starting from 6-aminopenicillanic acid, penicillins with all sorts of different side-chains have been and are still being made in their thousands. Among these are many acid-stable penicillins, of which phenoxyethyl and phenoxypropyl penicillins are examples which have found widespread clinical use. More important, new penicillins have been obtained which are resistant to the action of penicillinase and which therefore are active against bacteria against which benzylpenicillin is not effective, among them being the dangerous benzylpenicillin-resistant staphylococcus.

Two of these are widely used in clinical practice: 2,6-dimethoxyphenylpenicillin and 5-methyl, 3-phenyl 4-iso oxazolyl penicillin; the latter is not only stable against penicillinase, but also against acid, and can therefore be used orally for the treatment of benzylpenicillin-resistant staphylococcal infections.

The penicillin molecule has now been synthesized, after numerous unsuccessful attempts made over a period of more than ten years. The difficulty was to find conditions to bring about closure of the four-membered β-lactam ring in the synthetically accessible penicilloates (fig. 3, *3*). The action of all known ring-closing agents on penicilloates resulted in the opening of the thiazolidine ring with the concomitant formation of the penicillanic acids (3, *5*) containing the five-membered azolactone ring. Success was finally achieved by Sheehan and his collaborators, who employed a novel kind of ring-closing agent, the carbodiimides, which act in neutral aqueous solution, being hydrated to urea derivatives. The reaction leading to the synthesis of phenoxymethyl-penicillin from the corresponding penicilloate is shown below.

6-aminopenicillanic acid itself has been obtained by this method of synthesis, but the method of its preparation by enzymatic scission of benzylpenicillin is much simpler and more economical.

After twenty years of antibacterial chemotherapy, the penicillins are still the most powerful and least toxic antibacterial agents known. They are still the drug of choice in clinical infections with streptococci, pneumococci, meningococci, the spore-forming anaerobes, and the spirochaetes. The conquest of syphilis and tropical yaws, both caused by members of the latter group, marks one of the biggest triumphs of penicillin therapy. There is no sign that the effectiveness of penicillin as a chemotherapeutic agent has diminished in any disease caused by the above mentioned bacteria, with the exception of certain strains of staphylococci which do not respond to penicillin and have been observed to appear with increased frequency in hospital wards in many parts of the world.

The appearance of penicillin-resistant staphylococci has been interpreted erroneously by some observers as indicating that the staphylococcus had followed the well-known pattern of behaviour of other micro-organisms, which in the past have frequently developed resistance to drugs to which they were originally sensitive, for instance, that of spirochaetes against salvarsan, of gonococci against sulphonamides, and so on.

However, the true explanation of the phenomenon, which was real enough and has given serious trouble in clinical practice, was found to be on an entirely different basis. It is caused by the circumstance—which has no relation to the introduction of penicillin into medicine—that there exists in nature, and has always existed, a relatively high proportion of staphylococcal strains which produce the benzylpenicillin-destroying enzyme penicillinase (reaction I→III) and for this reason are insensitive to the action of benzylpenicillin. The capability of a bacterial strain to produce penicillinase is a genetically controlled factor and cannot be induced *ex novo* by penicillin, though penicillin can greatly stimulate the production of penicillinase in strains which are naturally endowed with the capability of penicillinase production. Penicillinase-producing staphylococci are frequently highly pathogenic and toxic.

If, in a hospital ward, patients infected with both benzylpenicillin-sensitive and penicillinase-producing (and therefore benzylpenicillin-insensitive) staphylococci are present, the usual course of events is that the penicillin-sensitive organisms will be eliminated by penicillin treatment and the infections caused by these will be cured, but the penicillinase-producing staphylococci will be left untouched and they will often spread to other patients in the same ward and cause a local epidemic of staphylococcal infection, which, of course, does not respond to benzylpenicillin. This picture gives the appearance of the staphylococci having developed resistance to benzylpenicillin during treatment, but in reality all that has happened is that the penicillin-sensitive staphylococcal strains have been eliminated by penicillin treatment and have been replaced by the genetically different penicillinase-producing staphylococcal strains. Cross-infections of this kind can be avoided by adhering to a rigid hygienic routine, but it must be remembered that normal persons, not obviously suffering from a staphylococcal infection, can be nasal carriers of pathogenic penicillinase-producing staphylococci, and may spread them.

The whole problem of infections with penicillinase-producing staphylococci has found a complete chemotherapeutic solution through the discovery of the penicillinase-resistant penicillins referred to above.

These substances are as effective in the clinic as they are in the test-tube, and have brought the benzylpenicillin-resistant staphylococcal infections under complete control.

Penicillin is a powerful bactericidal agent, acting in concentrations as low as 0·01 μg per ml, but kills bacteria only in media which will support their growth in the absence of penicillin. Investigation of the mode of action of penicillin has shown beyond doubt that it exerts its bactericidal action by interfering with the synthesis of a constituent of the bacterial cell-wall.

Penicillin possesses no toxicity, but soon

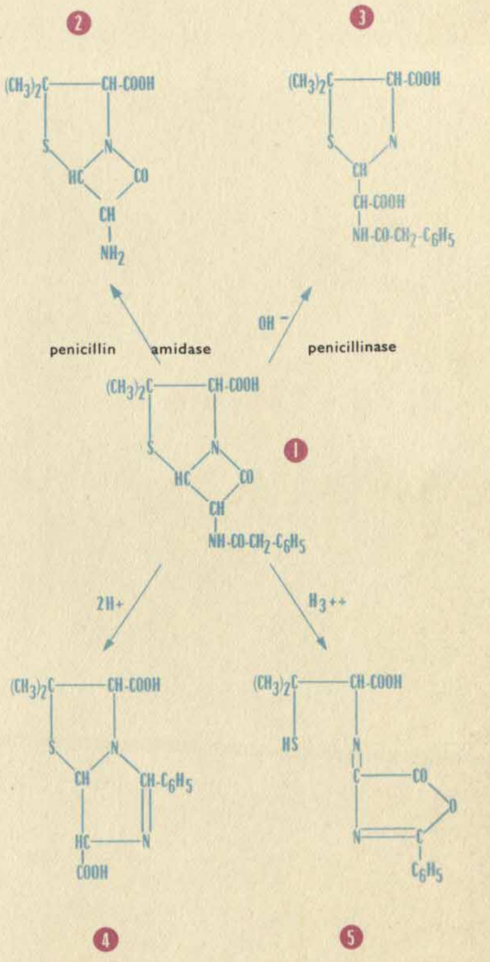


*Fig. 3. Benzyl penicillin (1) and its derivatives. From it, 9-aminopenicillanic acid (2) is obtained by the action of penicillin amidase, penicilloates (3) by penicillase; benzylpenicillic acid (4); penicillanic acid (5) with the 5-pointed azolactone nucleus.*

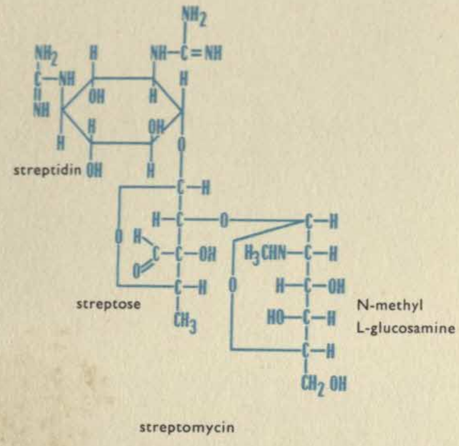


*Fig. 4. Chemical formula of streptomycin.*

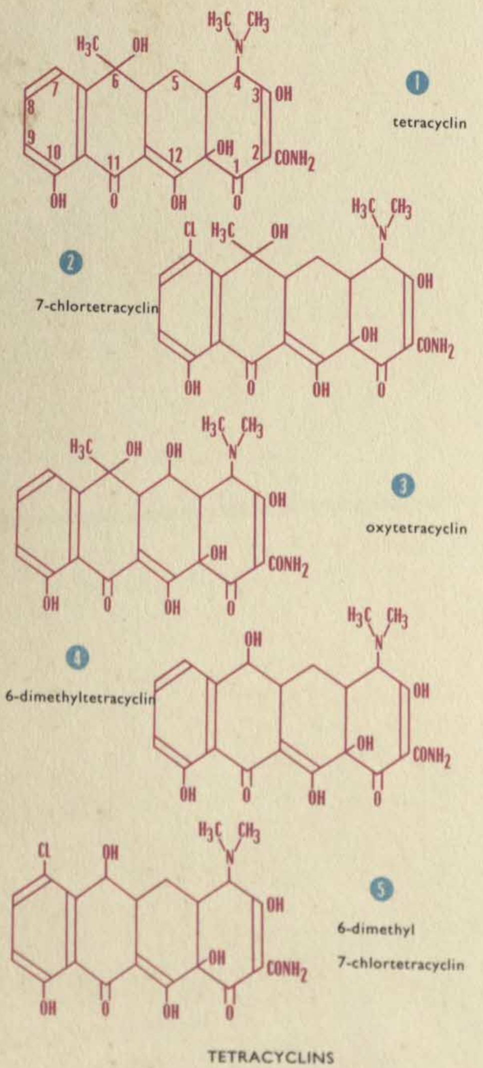


*Fig. 5. Formulae of the tetracyclin group.*

after the introduction into clinical use of benzylpenicillin, it was noted that a certain small percentage of patients were highly allergic to this substance, reacting with all the typical symptoms of allergic high sensitivity.

Benzylpenicillin was thus recognized as a potent allergen, and the same applied to the acid-stable phenoxymethylpenicillin. Evidence is now accumulating that the penicillins exert their allergenic power through the intermediate formation of the penicillanic acids (fig. 3) which react with proteins through their free SH groups, forming mixed S-S linkages, and through their azolactone ring, forming peptide linkages, principally with the free-end amino groups of the lysin residues.

## *Streptomycin*

Streptomycin was discovered in 1944 by Schatz, Bugie and Waksman as an antibacterial metabolite of *Streptomyces griseus*. It has the chemical structure of a trisaccharide, consisting of three portions: diguanidinoisinositol, streptose, and N-methyl-l-glucosamine (fig. 4). Streptose is one of the many new sugar structures which have come to light during the search for new antibiotics. Streptomycin is much less active than penicillin against the Gram-positive pathogens, but much more active against Gram-negative ones. Its most important property is its high activity against the bacillus of human and bovine tuberculosis. Clinically, many forms of tuberculosis, particularly the acute meningeal form, respond to streptomycin treatment; streptomycin represents the first effective chemotherapeutic drug against tuberculosis and as such has great historic importance. Naturally, not all forms of tuberculosis respond equally well to streptomycin; the chronic forms, in particular, with well-established tubercles into which the drug cannot penetrate, are more resistant to its action. However, in many such cases a combination of surgery with chemotherapy has led to successful treatment. Streptomycin has two disadvantages, which became manifest during its extended clinical use. First, on prolonged use over many months, which is often necessary in the treatment of tuberculosis, toxic symptoms appear, consisting in damage to the acoustic nerve and the vestibular system, causing nausea, vertigo and deafness. This difficulty was to some extent overcome by the use of dihydrostreptomycin, in which the free aldehyde group of the streptose moiety is reduced to the corresponding alcohol. Dihydrostreptomycin displays less chronic toxicity than streptomycin.

Secondly, streptomycin readily induces resistance in susceptible organisms, and it has been observed in many cases under treatment, both of tuberculosis and of infections with Gram-negative bacteria, that the micro-organisms which were sensitive to the action of streptomycin at the beginning of the treatment, became resistant to streptomycin during its course. The development of streptomycin-resistant strains can be retarded by the concomitant administration of the two other antitubercular drugs which were discovered after streptomycin: p-aminosalicylic acid, and isonicotinic hydrazide (isoniazide), both synthetic products.

Summarizing, it can be said that the introduction of streptomycin into medicine has, for the first time, made the chemotherapy of tuberculosis possible. Despite its defects, it is still extensively used, both alone and in combination with p-amino salicylic acid and isoniazide, and over the course of time it has not lost much of its clinical efficacy. It will continue to be used clinically as an antitubercular agent until a drug with much better properties, ie, one less toxic and less apt to induce resistance, is discovered.

## *Chloramphenicol*

Chloramphenicol has the structure (fig. 7) (D-(-) threo-2-dichloroacetamido 1-p-nitrophenyl, 1-3 propanadiol). The two unusual features of this structure are the presence of the nitrophenyl and dichloroacetyl groups, which have not been previously encountered in natural products. Chloramphenicol has a structure capable of chemical synthesis; several methods for its synthesis have been worked out and it is the only clinically important antibiotic produced commercially by synthesis alone.

Chloramphenicol was the first broad-spectrum antibiotic to be isolated. It has powerful activity against both Gram-positive and Gram-negative bacteria, and against the rickettsiae. Its use in medicine is widespread. It is of particular value against infections of the urinary tract with Gram-negative bacteria, against the common *Salmonella* infections of the intestinal tract, typhoid and paratyphoid fever, against whooping cough and chronic respiratory infections caused by *Haemophilus* strains, and against many forms of rickettsial diseases, such as scrub typhus, epidemic typhus, Rocky Mountain spotted fever and Q fever. Some toxic effects of chloramphenicol have been reported, mainly in the form of blood disorders, which are probably caused by the nitrobenzene group present in the molecule. These toxic effects are, however, very rare and have not seriously interfered with its clinical use. No reports of a serious decrease of efficacy of chloramphenicol owing to induced resistance in susceptible bacteria have been published.

## *The tetracyclines*

The tetracyclines are a group of antibiotics characterized by a chemical structure consisting of four condensed six-membered rings, closely related to the hydrocarbon naphthacene. They differ in the substitutions in the ring. The main tetracyclines in clinical use are chlortetracycline, oxytetracycline, 6-demethylchlortetracycline, 6-demethyltetracycline, and tetracycline itself (fig. 5).

The tetracyclines are produced by fermentation methods; the demethylated products by removal of the methyl groups by chemical methods. They are broad-spectra antibiotics with an antibacterial range very similar to that of chloramphenicol. Like chloramphenicol, they are widely used in clinical medicine for the treatment of the same infections. In many cases, bacterial strains sensitive to chloramphenicol are also sensitive to the tetracyclines, and in this case both are equally effective clinically. It must, however, be remembered that there exist in nature quite a large number of Gram-negative organisms which are resistant to chloramphenicol and the tetracyclines. Some of these bacterial strains may be sensitive to the tetracyclines, but not to chloramphenicol, and vice versa, and under these circumstances they are complementary to each other. Some strains, however, are equally resistant to both types of antibiotics, and in these cases clinical treatment with either of them is ineffective. No serious toxic effects of the tetracyclines and no emergence of bacterial resistance to their action has been reported, though in some hospital wards sensitive strains may temporarily be replaced by resistant ones.

One undesirable side-effect of both the tetracyclines and chloramphenicol is that in some cases the balance of the intestinal microbial flora is changed, with the result that an overgrowth of *Monilia*, a yeast-like organism, takes place and causes irritation. In the course of time, however, the normal flora balance is restored.

## *Antibiotics of limited application*

### 1. *Antibiotics against penicillin-resistant staphylococci*

Before the discovery of the penicillinase-resistant penicillins there was an urgent need to find an antibiotic to combat the penicillin-resistant staphylococci, which, as was stated above, had begun to cause serious trouble in many hospitals. Several such substances were discovered, but none gave the perfect answer to the problem, and now, with the availability of the very effective new penicillinase-resistant penicillins, they are largely obsolete as clinically useful drugs. In view of the fact, however, that the elucidation of their chemical structure has shown them to be novel types of compounds of considerable biochemical interest, they will be briefly listed.

(a) *The macrolides.* This group of substances occupies, chemically, a position between sugars and fatty acids. The common feature in the structure of the macrolides is a large lactone ring (consisting of a chain of 11 to 17 carbon atoms) and novel types of sugars, some of them nitrogen-containing. A large number of macrolides has been isolated in pure crystalline form and their structure elucidated. Among those which have found clinical use are erythromycin, carbomycin, oleandomycin, and spiramycine. The structures of erythromycin and carbomycin are indicated below. The macrolides are active against Gram-positive bacteria, but are very insoluble in water and therefore do not readily diffuse. They also induce resistance in sensitive bacteria.

(b) *Novobiocin.* This antibiotic has the following structure. It is a derivative of 3-amino, 4,7-dihydroxy, 8 methylcumarine, in which the amino group forms a peptide link with 4-hydroxy, 3-isopentenylbenzoic acid and the 7-hydroxy group forms a glucosidic linkage with a novel type of sugar, novobiose, which carries an urethane grouping. Novobiocin is active against the Gram-positive organisms, but its activity is not very high and it induces resistance with great rapidity.

(c) *Kannamycin.* This antibiotic resembles streptomycin in its chemical structure. It has similar pharmacological and antibacterial properties, and has been used in penicillin-resistant staphylococcal infections, as well as in tuberculosis. Its main drawback is its toxicity.

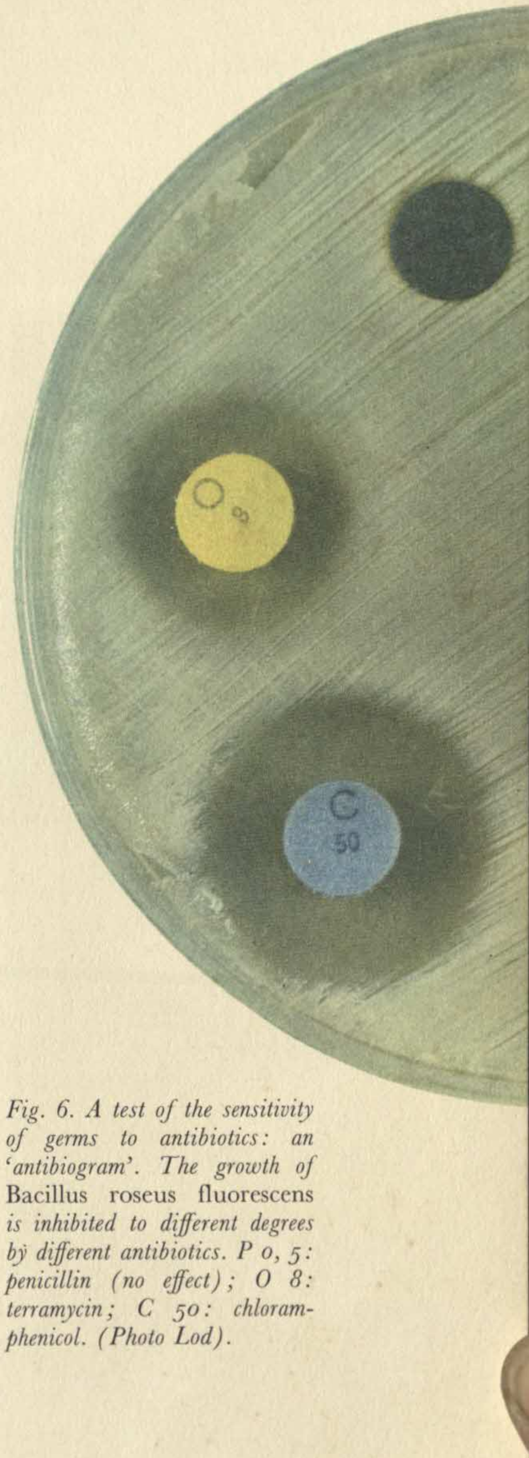
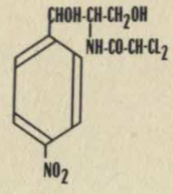


*Fig. 6. A test of the sensitivity of germs to antibiotics: an 'antibiogram'. The growth of* Bacillus roseus fluorescens *is inhibited to different degrees by different antibiotics. P 0, 5: penicillin (no effect); O 8: terramycin; C 50: chloramphenicol. (Photo Lod).*



chloramphenicol

*Fig. 7. Chloramphenicol or chloromycetin.*

*Fig. 8. Micropulverized benzathine penicillin. (Photo Lod, taken in Usines Rhône-Poulenc).*

2. *Antibacterial peptides*

A large group of antibiotics produced by bacteria is constituted by the cyclic polypeptides. Historically, this group has played a very important role in two respects. First, two polypeptides, discovered in 1939 by Dubos and his collaborators, and termed gramicidin and tyrocidin, were the first crystalline antibiotics of bacterial origin to be isolated; secondly, one of the gramicidins was the first natural polypeptide of which the complete sequence of amino acids was elucidated by means of the method of partial hydrolysis, later applied with such outstanding success to the elucidation of the structure of much more complicated polypeptides and high-molecular proteins.

In structure, gramicidin Sn and tyrocidin A are cyclic decapeptides of which one half is identical in both substances. A noteworthy feature of these formulae is the presence of the unnatural d-form of some of the amino acids. In tyrocidine A both the natural and the unnatural forms of phenylalanine are present. Tyrocidine A differs from tyrocidine B in one amino acid constituent; phenylalanine in tyrocidine A is replaced by l-tryptophane in tyrocidine B.

The antibacterial polypeptides have only a very limited practical application in treatment. The crude mixture of gramicidin and tyrocidines, termed tyrothricin, has been used, and is still being used, as a local antiseptic.

One group of antibacterial polypeptides, the polymixins, have found limited clinical use in the treatment of infections caused by *Pseudomonas pyocyanea*, but they must be administered with considerable caution because they exert a nephrotoxic effect. The polymixins are cyclic peptides characterized by the presence of α, γ-aminobutyric acid as one of their amino acid constituents, and of a fatty acids side chain.

3. *An anti-tubercular antibiotic: Cycloserine*

Cycloserine displays considerable antitubercular activity. It has been used with some success in some cases of human tuberculosis, but has toxic effects on the central nervous system.

4. *Antifungal antibiotics*

(a) *Griseofulvin*, produced by the mould *Penicillium griseofulvum*, has been shown to be effective, when given orally, in dermatomycoses (ring-worm infections) caused by species of *Trichophyton*.

It is so far the only systematically active agent against pathogenic fungi. Moreover it does not appear to have any toxic effects.

(b) *Antifungal polyenes*. A number of antibiotics, containing a series (4 to 7) of conjugated double bonds have been found which display activity against yeasts and fungi. Among those that have been found to have limited clinical application, mainly topical, in *Candida* infections, are nystatin, rimocidine, candidine, candicidine, trichomycin, and amphothericin.

All of them are rather insoluble in water, unstable and too toxic for systemic use.

It is abundantly clear that the discovery of the antibiotics and their chemotherapeutic action has signified an immense advance in therapeutic medicine and the gain derived from it is likely to be of permanent value. All the great categories of the most dangerous and common bacterial infections, ie, those caused by the most important Gram-positive and Gram-negative pathogens, the mycobacteria and the rickettsiae, have become amenable to chemotherapeutic treatment. Among the few bacterial infections which have remained almost entirely resistant to chemotherapeutic treatment with antibiotics—or, for that matter, to any other antibacterial agent—are those caused by the Gram-negative *Pseudomonas pyocyanea;* they continue to be a source of considerable trouble in hospital wards and make imperative an intensive search for an effective antibacterial agent.

The danger that the antibiotics would, in a short space of time, lose much of their effectiveness owing to the development of resistance to their action by susceptible micro-organisms, has fortunately turned out to be less serious than was feared, but the possibility that induced resistance may eventually present a serious problem must never be lost sight of.

From the practical point of view, a more important and greater menace to therapy than induced resistance is presented by the fact that some bacterial species, particularly the Gram-negative ones, contain a high percentage of strains which are resistant to the broad spectrum antibiotics, though the majority of the strains belonging to these species show high sensitivity to them. Against those members of these species no effective antibiotic therapy exists. There is a very real danger that in the course of time these strains will gain the upper hand and replace the sensitive strains. This possibility provides a continuous challenge to research.

# Chemical treatment of cancer

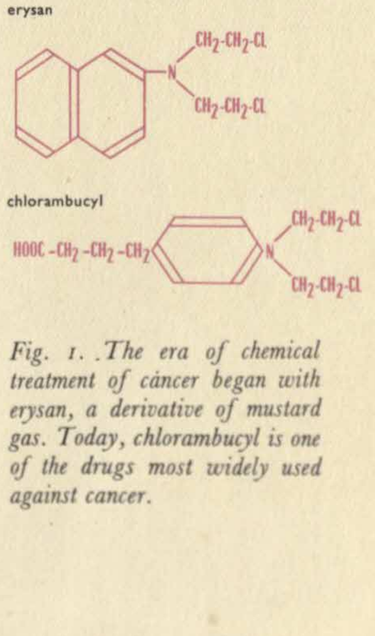
*Walter DAVIS*

*The problem of the cure of cancer confronts all those who seek its solution with many fundamental difficulties, and although in the last fifteen years some progress has been made, it is as well to review the problem itself, so that any claims for advance may be measured against this yardstick. In this chapter we shall be concerned only with chemotherapy, but the immunologists and virologists are also deeply involved in the search.*

Theoretically, the search should be for a drug that can eradicate the cause of malignant growth. As almost all that is known about carcinogenesis involves exogenous causes, and very little indeed is yet known of endogenous causes, the possibility of basic cancer *cures* by drugs remains distant. However, from empirical studies guided by a general knowledge of the biological mechanisms involved in growth, it has been possible to design drugs that are capable of stopping the growth of experimental animal tumours and, by selecting the best of these, to achieve some important alleviation of symptoms in one group of malignant diseases, the leukaemias. Clinical claims are made for drug efficacy in cases of some other cancers too, but these are still only a small percentage of the total cases of cancer presented to clinicians. For the rest, with the exception of the group of hormone-dependent tumours—which respond to treatment with hormones—chemotherapy can add little at present to surgery and irradiation, which are the major forms of cancer therapy. Nevertheless, the clinical problems presented by metastatic[1] tumours, by inoperable tumours, and by radiation-resistant growths provide an urgent and powerful incentive to the continuing search for anti-cancer drugs.

The present limitation of cancer chemotherapy exists for very obvious reasons. Antibacterial drugs are designed to destroy an invading organism that has a quite different structure, nutritional requirement, and metabolism, and hence quite different sensitivity to drugs from that of the human body that has been invaded. The cancer cells that make up the tumour mass may appear very different from the normal cells from which they have arisen, but because there is so little difference in their fundamental metabolism, both normal and malignant cells are susceptible to attack by the growth-inhibiting drugs. The problem, then, is one of selective destruction of malignant cells while leaving their environment of normal cells unharmed. How is this task being approached at the present time?

It is postulated that, in response to an often quite unknown stimulus, a normal cell undergoes some apparently irreversible change and subsequently gives rise on cell division to two daughter cells that are malignant, and whose progeny will also be malignant. In other words, malignancy becomes a genetic charac-


erysan

chlorambucyl

*Fig. 1. The era of chemical treatment of cancer began with erysan, a derivative of mustard gas. Today, chlorambucyl is one of the drugs most widely used against cancer.*

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(1) Metastatic: *arising by the transfer in the blood stream of malignant cells from the primary cancer growth.*

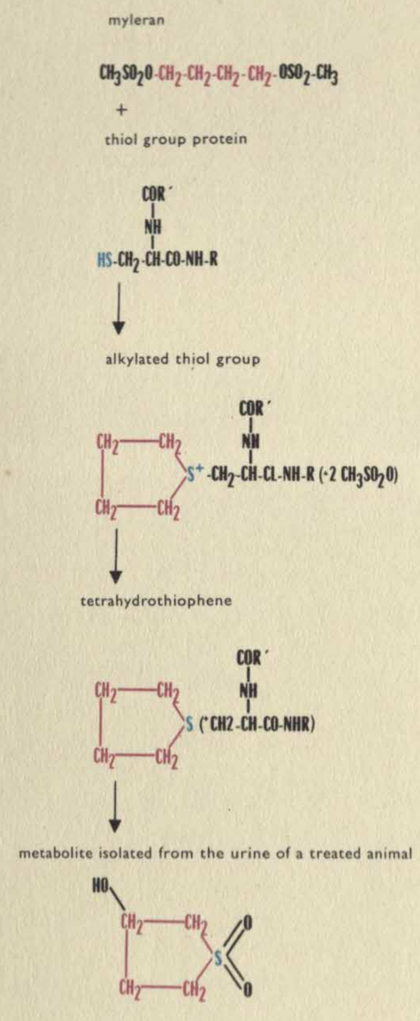


*Fig. 2. Alkylation of a protein of the thiol group by myleran.*

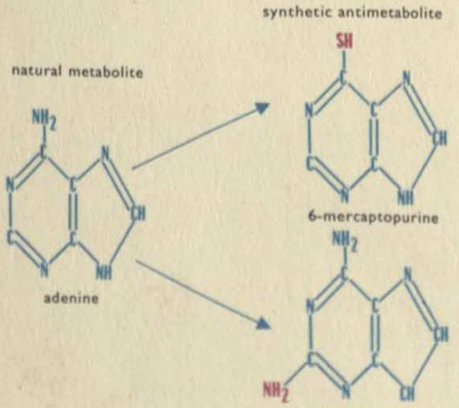


*Fig. 3. One of the most active antimitotic agents is 6-mercaptopurine, which inhibits cellular growth.*

teristic of the cell and it is the genetic material, in the cell, principally the nucleoprotein of the chromosomes, that has become the main target for chemotherapeutic attack. More specifically, it is the deoxyribonucleic acid (DNA) component, that carries much of the genetic information. There are grounds for believing that anti-cancer drugs achieve their effect by impairing DNA synthesis, so that it either fails to achieve the degree of organization necessary to allow normal cell division to proceed at all—this is growth inhibition—or else the genetic formation inherent in its chemical structure is altered—this is mutation.

Biologists have demonstrated both these effects experimentally. For example, male rats can be made temporarily infertile with certain anti-cancer drugs, through inhibition of spermatogenesis—and spermatozoa are composed almost entirely of DNA. These drugs are capable too of inducing visible mutations in *Drosophila melanogaster*, the fruit fly, and in bacteria. There are also chemical studies that substantiate the action of these drugs on DNA. After administering radio-isotope labelled drugs, fragments of DNA are found chemically combined with such drugs; other chemical compounds have been found incorporated by normal metabolic processes into nucleic acid, producing biologically 'fraudulent' material.

These effects, which have been produced by a wide range of potential anti-cancer drugs, have also been used to demonstrate quantitative differences in the biological effectiveness of the drugs, but they do not yet indicate the ability of any known drug to act selectively against tumour cells without producing toxic effects elsewhere in the body.

There are theoretically feasible routes to the establishment of this fundamental selectivity. The first seeks to exploit differences, which need be only quantitative, in the enzymic complement of normal and malignant cells. One drug, cyclophosphamide, has already been used clinically. Although in its intact state it is inactive, it could release an active product in the body after breakdown by enzyme action. Subsequent biological testing has indicated, however, that the enzymes involved in this process are not obviously different in normal and malignant cells, and that the drug's activity is not selective. The general approach, nevertheless, still remains valid and may yet be rewarded with some success.

Another attempt at selectivity seeks to take advantage of an observed physical characteristic of malignant cells. Because of certain changes in the way enzymes in malignant cells break down glucose, tumour tissue appears to be more acidic than the normal tissue from which it has arisen. This difference is not large, but may enable chemists to design drugs carrying basic groups that would concentrate in the more acidic malignant cells.

Meanwhile, awaiting biological clues that may point to more selective drugs, the chemist has synthesized on a semi-rational basis a range of drugs that provide the clinician with the means of achieving symptomatic relief in many of the different forms of leukaemia and related conditions.

The first drug in the field, known as 'nitrogen mustard'—methyl di-2-chloroethylamine—was, paradoxically, a chemical warfare agent. Studies of the physiological action of this poison showed that, apart from being a powerful vesicant[2], it exerted a profound depressant effect on the blood-forming tissues in the bone marrow and consequently on the circulating blood. It was only a short step from here to the introduction of this drug, known as HN2 or mustine, in the treatment of leukaemias, and now, fifteen years later, it is still one of the standard drugs used in the treatment of Hodgkin's disease.

Hundreds of derivatives of this parent compound have been made in the intervening years, firstly in an effort to reduce the acute toxicity that accompanied the anti-leukaemic activity, and secondly, so to alter the molecular structure carrying the dichloroethylamino-group that the drug might become more specific in its action.

When the dichloroethylamine derived from β-naphthylamine was tested it was found to be still an effective drug, but it was no longer powerfully vesicant and, in fact, as 'erysan' it was given by mouth in clinical trials, in marked contrast to HN2, which demanded the most careful intravenous injection if its administration was not to produce painful damage to skin and vein.

Subsequently drugs were synthesized in which the carrying structure included various basic and acidic side chains. Of these, chlorambucyl has proved to be of value clinically; it may owe its success to the detergent-like[3] property that the terminal acid group confers, facilitating both transport in the body fluids, and cell and nuclear membrane penetration. Amino acid carriers have also provided useful drugs, like melphalan (L-sarcolysin) and their derived peptides, which may owe their effectiveness to similar properties. Alternatively, the amino acid[4], a molecule occurring naturally in the structure of the cell, might become involved in some metabolic process, so that the nitrogen mustard part of the molecule is built into some vital tissue structure, or perhaps it can anchor the molecule by a chemical or physical bond to a protein surface until the chloroethyl group has reacted.

It is important to note at this point that these 'nitrogen mustards' are rare examples of drugs that exert their effect by actual chemical combination with susceptible points in living cells, and, as we have already mentioned, products of their reaction with DNA components have been identified. This type of chemical combination is characterized as 'alkylation',[5] and a development of chemotherapy has been to examine, as anti-cancer drugs, the other chemical compounds known to be capable of alkylation under physiological conditions. This research has produced the di-epoxides, the triethyleneimines 'TEM' and 'ThioTEPA', and the dimesyl esters, of which 'myleran' is the most widely used and valuable member. All these are classed as alkylating agents, and all require at least two alkylating groups in the molecule to exert the recognizable anti-leukaemic effect. What the significant points of attack are in the living organism is not yet certain, but it has been shown that 'myleran' is capable of alkylating a protein thiol[6] group, first with one chain then with the other, to form a cyclic compound, tetrahydrothiophene, metabolites of which have been isolated from the urine of treated animals. Other workers, we have said, have been able to demonstrate the alkylation by nitrogen mustard of two neighbouring guanine bases in DNA, but whether these are the necessary reactions to produce the observed biological effects remains speculative. These are, after all, highly reactive compounds and it seems likely that many nucleoprotein precursors might be susceptible to alkylation before they are built into the giant molecules that make up chromosome material. It is here that the alkylating drugs simulate the drugs known as 'antimetabolites'.

The biochemistry of growth involves above all the rapid and accurate synthesis of nucleic acids. This very complex process involves the building up of nucleotides[7] of a molecular weight of about 400 into long ordered chains of much higher molecular weight—variously estimated as six million or more of DNA. Anti-metabolites are drugs designed as spanners that can be thrown into the works in this essential growth process. Synthetic purines and pyrimidines, whose molecular structures are subtly different—maybe by only one atom—from the naturally occurring bases, have been found to be capable of inhibiting growth at very low concentrations. Perhaps in some cases they are actually incorporated into the giant molecular chain, whose function is thus impaired, or they may divert the enzymes that control the synthetic processes from their normal function and so prevent the building up of new DNA molecules. But whatever their mechanism of action, from among the anti-metabolites clinicians have been able to make use of certain compounds as anti-cancer drugs. 6-mercaptopurine is most widely used in the treatment of some forms of leukaemia, and seems outstanding among a very large number of purine and pyrimidine analogues that have been tested. Very many of them display experimental activity, but very few offer any clinical advantage.

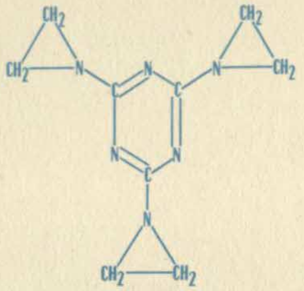
There is one other drug in this field, methotrexate, which is of clinical importance, as it is useful in the treatment of acute leukaemia in children. Its ability to inhibit growth appears to depend on blocking the normal synthesis of purines and pyrimidines.

The vast new field of antibiotics has been scoured for anti-cancer drugs. Azaserine and diazo-norleucine were found to have some anti-tumour activity, but only actinomycin D has any widespread clinical application.

Thus only a few drugs of accepted clinical value have been found out of many hundreds that have been shown experimentally to be growth inhibitors, but the experimental work has not been in vain, for it has contributed a great deal to the fundamental knowledge of the biology, as well as of the chemistry, of cell growth and cell division, and something to our knowledge of carcinogenesis. There may yet be a thread from here back to that real target of cancer research, the stimulus that induces the primary malignant change.

TRIETHYLENEIMINES

TEMtrietramine



ThioTEPA

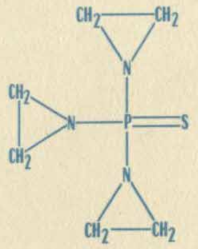


*Fig. 4. Triethyleneimines act directly on the metabolism of cancer cells by substituting themselves for normal metabolites.*

(2) Vesicant: *blister-producing.*

(3) Detergent: *a compound capable of dissolving in both fatty and aqueous solutions.*

(4) *The* amino acid *may act by making the dichloroethyl radical appear in an essential tissue constituent, or by fixing the molecule by a chemical or a physical bond to the surface of a protein until the chloroethyl group has reacted.*

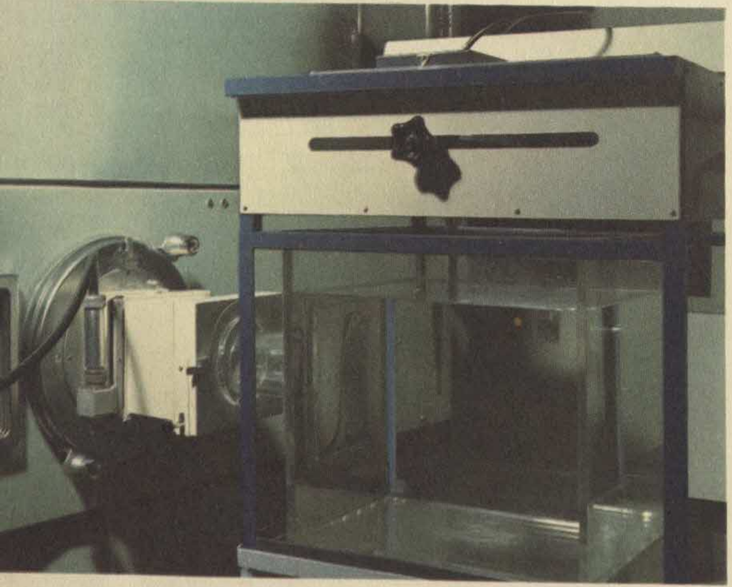
(5) Alkylation: *a general type of organic chemical reaction, often used in the laboratory, for adding a simple or substituted hydrocarbon group on to another molecule.*

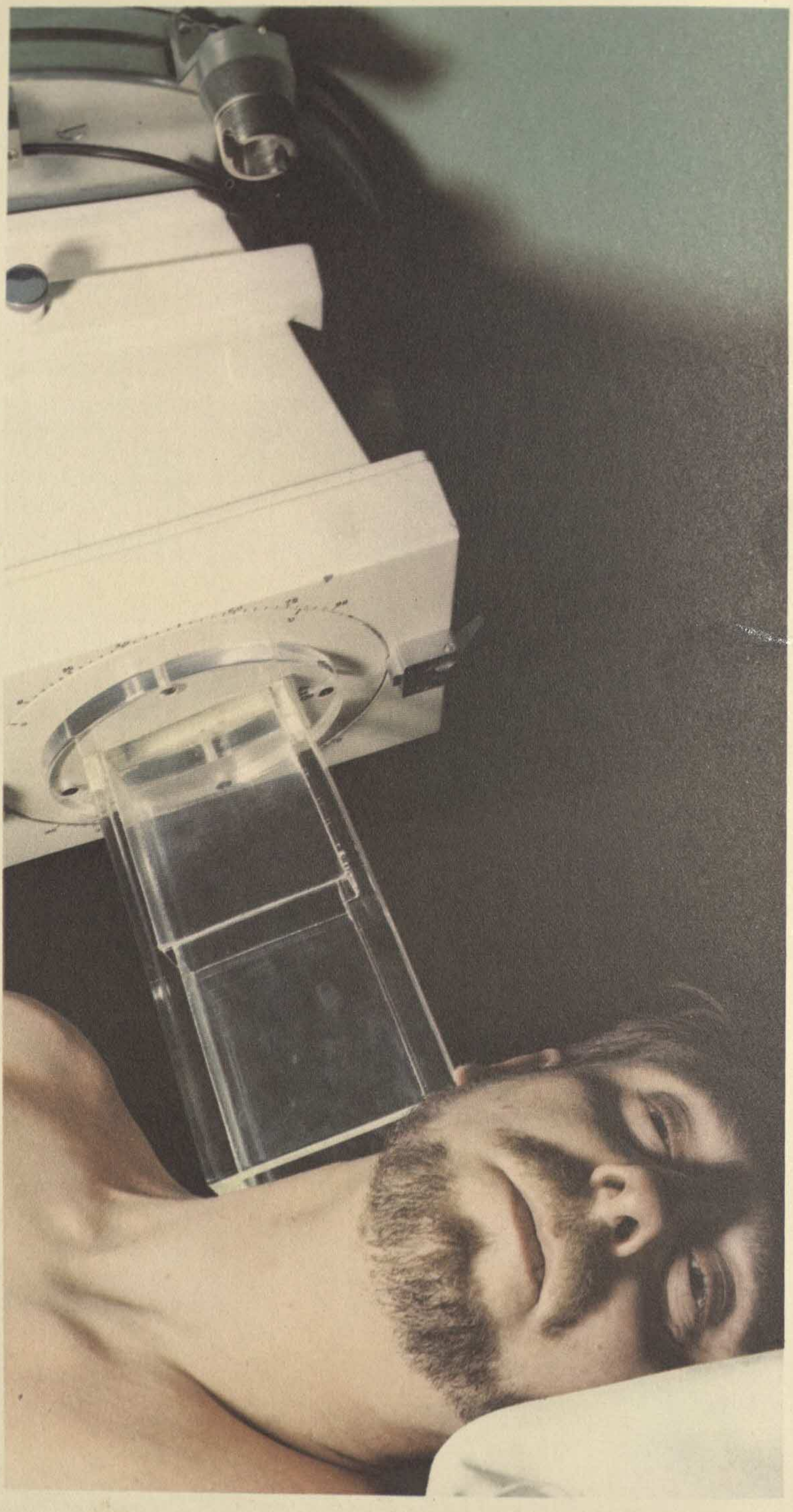
(6) Thiol: *a molecule containing a reactive sulphur atom linked with hydrogen on one side and carbon on the other.*

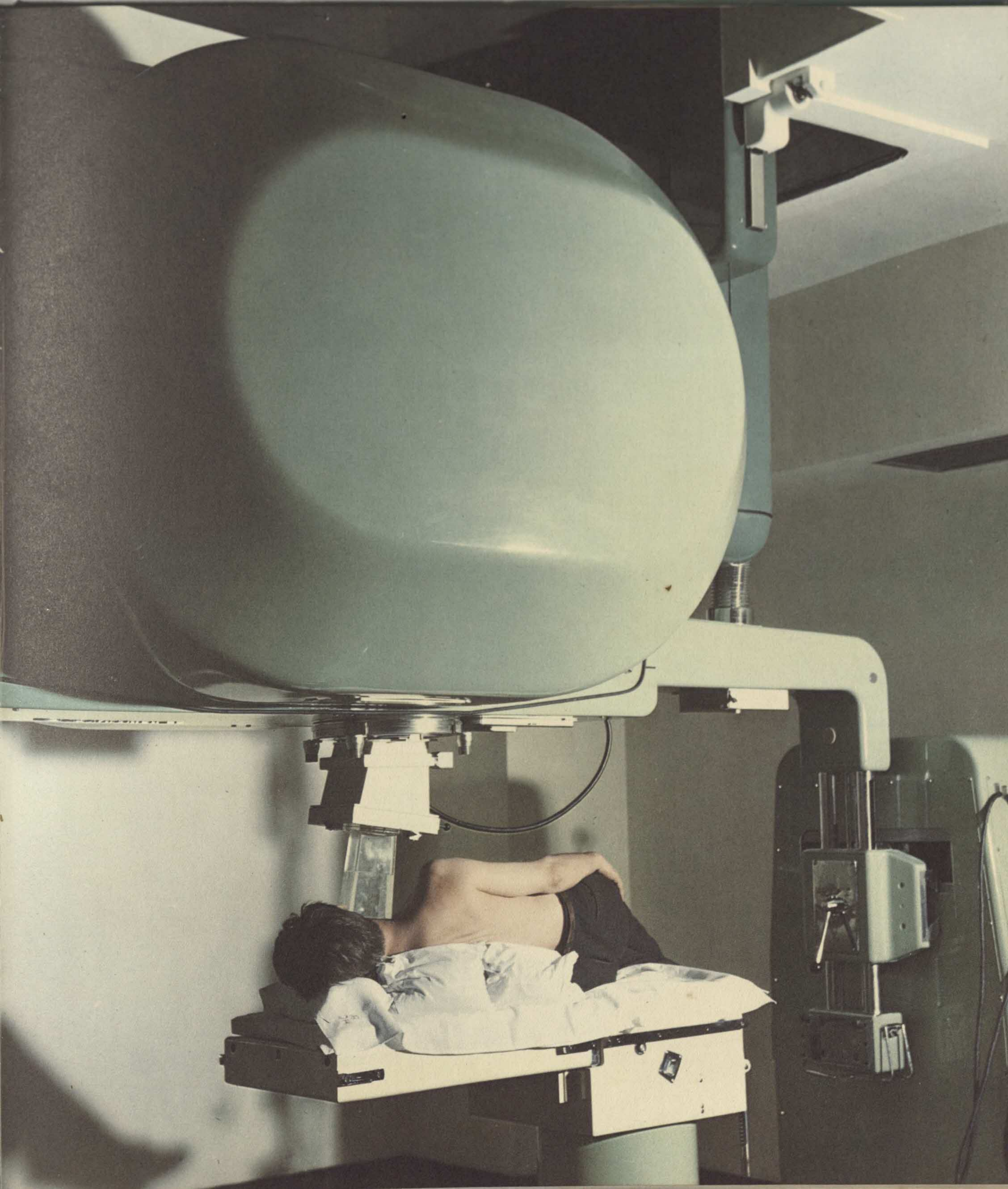
(7) Nucleotide: *the building unit, consisting of a purine (or pyrimidine) base linked to a sugar molecule (deoxyribose) which in turn is linked to a phosphate group, tens of thousands of which are linked to make up the giant DNA molecule.*

# *The betatron*

*Radiotherapy is still one of the methods in most general use for the treatment of cancer. Here are shown various aspects of the betatron in the Hôpital Curie in Paris. From top to bottom and from left to right: the control desk; the 'explorer' which makes it possible to displace the ionization chamber and to measure the dosage; electron treatment by means of a plexiglass 'localizer' applied to the skin of the patient; general view of the irradiation equipment.*







# The destruction of cancerous cells

## *Alfred GLUCKSMANN*

The differences between normal and malignant cells of the same individual concern their behaviour and functional potentialities rather than their constitution and requirements and are quantitative rather than qualitative. This similarity between cancerous and normal tissues is the reason why so far no 'magic bullet' has been found which will seek out only the unwanted cancerous structures and leave uninjured the normal tissues and organs from which the neoplasm has arisen.

Indeed, cancer cells resemble their normal brothers often more than they do other cancer cells as regards morphology and physiological behaviour. In skin cancers, for instance, as in the normal epidermis, cells combine to form a tissue, are capable of some degree of horn formation and remain sedentary for very long periods; the cells of cancers arising in the precursors of white blood cells (leukaemia) are essentially individual, very mobile cells which quickly spread through the body and do not combine to form a tissue. Thus cancer cells inherit to some extent the normal characteristics of the tissues in which they originate; they retain some of the characteristics of the epidermis, the breast, the prostate and the thyroid, but differ from the normal tissue as regards the capacity for functional specialization (differentiation), the rate of cellular reproduction, the acquisition of invasive properties and their failure to respond to the regulatory controls of the organism over its tissues and of the organs over its cells.

Cancers vary in their degree of deviation from the normal prototype and the highest degree of deviation, which may be both morphological and/or functional, is termed 'anaplasia'. Generally, the more anaplastic the tumour looks, the more malignant it is as regards the destruction of normal tissue and rate of proliferation. Anaplastic tumours prefer the tonsil, tongue or pharynx, while they occur only rarely in the skin and lip, where differentiating carcinomas predominate.

Tumours develop in stages and only gradually acquire 'autonomy', which may be defined as a relative independence of the body's regulatory mechanisms. Thus tumours arising in organs subject to endocrine influences may respond to stimulatory and inhibitory hormonal control. Use can be made of this phenomenon as, for instance, in the oestrogen therapy for prostatic cancer, the use of radioactive iodine in the treatment of cancers of the thyroid, the use of oestrogens or of androgens, or in late stages of adrenalectomy and hypophysectomy, in breast carcinoma. In all these instances the inherited normal characteristics of the cancerous tissues are exploited for therapy. Naturally, the radioactive iodine is picked up also by the normal parts of the thyroid and causes destruction by irradiating normal as well as malignant thyroid cells from within. The loss of thyroid function can be compensated by the administration of hormones. Anaplastic tumours of the thyroid fail to take up iodine and are thus beyond the scope of this form of treatment, which can deal successfully even with disseminated responsive thyroid cancers.

As long as the cancers are localized, surgery and radiation, either alone or in combination, can be employed successfully. The rapidly spreading tumours present a more difficult problem since their metastases cannot be localized accurately and removed or destroyed. Chemotherapeutic and immunological methods are being tried for such cases. The immunological methods exploit antigenic differences between the normal and malignant cells of the same individual and of the same type of tissue.

Chemotherapy aims mainly at cellular proliferation of the neoplasms by using drugs which upset the process of division and cause the death of the daughter cells, or by preventing the synthesis of substances necessary for cellular reproduction. A great variety of such drugs is available, but they are toxic for all cells undergoing division, whether normal or malignant. The rate of cellular proliferation in some normal organs, such as the blood-forming tissues, the intestine and the gonads, may equal that of neoplasms. The toxicity for these organs limits the dose which can be safely given. Tumour cells, like bacteria, can adapt themselves to the absence of substances necessary for cell division and learn how to deal with the presence of antimetabolites. This phenomenon can be used therapeutically by teaching tumour cells to metabolize a substance and then to offer it this substance combined with an antimitotic compound. By splitting this compound the cell poisons itself.[1]

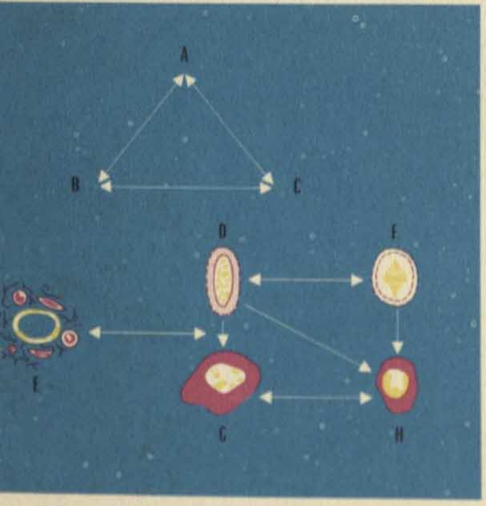


*Fig. 1. This diagram illustrates the correlations that exist in a tumour between the parenchymatous cells and the layer formed by the supplying vessels, (E); A, organic factors; B, focus of the tumour; C, parenchyma of the tumour; D, a stock cell that may either divide (F) or become differentiated (G) or degenerate (H).*

(1) *In order to protect normal tissues from the necessary dosage of the toxic agent, the latter is injected into an artery supplying the tumour, care being taken to block the venous drainage away from it. The tumour then absorbs almost all the drug; whatever gets into the circulation is less concentrated. This technique can, however, be used only in cases where the tumour has been accurately located.*

(2) *This phenomenon is not without analogy with heat-burns, the extent of which influences the formation of scar tissue. By focusing the ionizing beam in such a way as to multiply the*

Continued on next page

The dosage of toxic agents to normal tissues can be reduced by injecting the chemicals into the arteries supplying the tumour and temporarily inhibiting the venous flow from the cancer. Thus the tumour gets most of the dose and there is less overspill into the general blood circulation. This method can be used only when the neoplasm is suitably localized in one region of the body.

For more or less localized cancers radiotherapy in its various aspects remains the method of choice. The action of all forms of ionizing radiations are essentially the same, though there may be practical advantages in preferring radiations of supervoltage X-rays to conventional X-rays in the use of radium applicators in various forms for the treatment at various sites. Since radiation affects all tissues, the tolerance of the normal tissues limits the dosage which can be delivered to the tumour. Increasing the area and volume of normal tissue lowers the limit of tolerance,[2] much as the size of the thermal burn influences the chance of repair. By directing radiation through a number of fields at the tumour, the dose to it can be increased relative to that of overlying normal structures. Great care is required in choosing these fields to avoid overlap, and with it 'hot points' or gaps and under-dosage. Injury of normal tissues is also lessened by giving the treatment in numerous small doses over a long period of time instead of in a single large dose. For their repair the normal parts can draw on the help from adjacent unirradiated 'like' structures, while the tumour has no such external assistance.

The mechanism of action of radiation can be explained with the help of fig. 1. The cellular population of the tumour is represented in various phases of activity; the 'stock' cell, capable of all the other activities, is a potentially dividing, potentially differentiating, or potentially degenerating cell, but at a given moment is in a 'resting phase'. After a division (mitosis) into two daughter cells, these return to the resting phase and may subsequently divide and give rise to further stock cells. In some tumours the cells can differentiate, ie, form a special substance (such as horn (keratin), mucin, pigment, bone, cartilage) or secrete hormones. In forming keratin, for instance, the cell loses its capacity for proliferation and becomes sterile. The process of differentiation is never as complete as in the normal prototype. The reason why some tumours are capable of some degree of functional specialization while others are not, is yet unknown. The stock cell, like the dividing and to a lesser extent the differentiating cell, will degenerate and die if the environmental conditions become unfavourable.

The dependence of the tumour parenchyma (the cellular population) on the tumour bed, which is formed by the supplying normal vessels and cellular plus fibrillar supporting stroma, is indicated on the left of the diagram. The type of tumour bed tends to vary with the type of the tumour. Where the tumour is adequately nourished, the proportion of viable, ie, of actual and potential dividing cells to the non-viable differentiating and degenerating cells, will be high, but will decrease in favour of the latter if the environmental conditions deteriorate. At the advancing edge the conditions for growth are good, while in the more central and usually older regions the conditions are poor and the tumour tends to become necrotic. Naturally, the growing foci (strands of cancer) are the most dangerous and the most important regions to eliminate. The tumour parenchyma as well as the tumour bed are subject to systemic influences of the host and also influence the host systemically,[3] as we shall see later on.

Radiation affects the tumour parenchyma and the tumour bed, and through them indirectly the host. In all tumours radiation arrests mitosis, at least temporarily. On attempting division the irradiated cells may degenerate immediately or die after an abnormal division. Some cells may be able to divide at least three or four times before they degenerate. This delayed sterilization may be accounted for by the exhaustion through mitosis of some essential substance stored in the cell at the time of exposure. As a result of radiation injury, the cell cannot replace this substance, possibly because of some damage to the blueprint in the chromosomes. The 'mitotic' effect of irradiation can be achieved with small doses and may be revealed only when the attempt at division is made.

Some of the resting cells are killed and fatal injuries increase with the dose of irradiation. In some tumours the stock cells are stimulated to form keratin or some other specialized substance, depending on their inherited normal potentialities. Keratin formation renders the cells sterile and thus this radiation-induced change helps to slow down the growth of the tumour and to eliminate it. This action is one of the most important mechanisms of radiotherapeutic cure and depends on the ability of a given tumour to respond with increases in extent and degree of differentiation.

*irradiated fields, it is possible to increase the threshold of radiation tolerated by normal tissues beneath the tumour. This technique necessitates careful selection of the irradiated fields; it is essential to avoid their overlapping, which would lead to the production of 'hot spots', and of 'blank spots' where the dosage would be insufficient.*

(3) *The conditions for development are optimal on the attacking front of the tumour and less favourable in the central region, which is generally older and undergoing necrosis. The regions of active growth are the most important to eliminate. Both the layer and the parenchyma of a tumour are subject to the general*

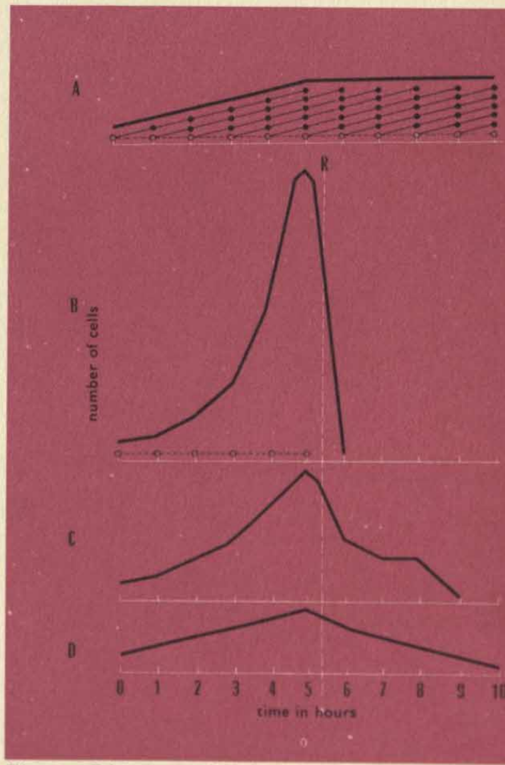


*Fig. 2. Diagrams showing the relations between the speed of regression of a tumour and the growth of tumour cells. A, total population of the covering surfaces in a state of equilibrium. B, a tumour formed entirely of stock cells capable of division. C and D, tumours with differentiation. The results of irradiation (the vertical line R) clearly show the sensitivity of cancer cells to radiation.*

Continued from previous page

*physiological condition of the host (systemic factors), and conversely their presence reacts on the host's metabolism.*

(4) *In an anaplastic tumour, the change of volume is the result of short-lived stock cells, and shows itself relatively early. In more highly differentiated tumours a formation intermediate between normal skin and an anaplastic tumour is seen.*

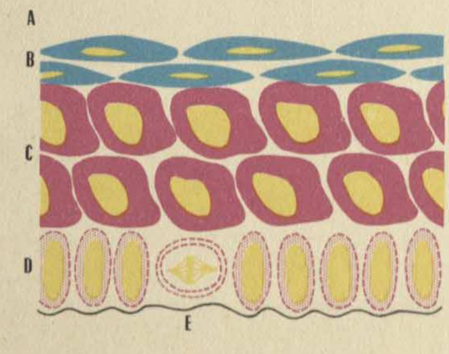


*Fig. 3. Diagram of normal epithelial tissue in equilibrium. A, exfoliated superficial cells. B, horny (keratinized) cells. C, differentiated cells. D, stock cells. E, mitosis.*

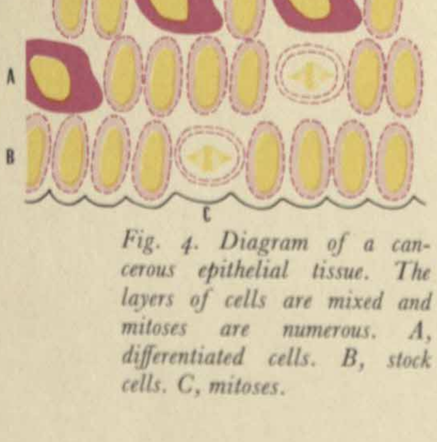


*Fig. 4. Diagram of a cancerous epithelial tissue. The layers of cells are mixed and mitoses are numerous. A, differentiated cells. B, stock cells. C, mitoses.*

The effects of radiation on the tumour bed can be summarized as the induction of an inflammatory reaction with vascular dilatation, stagnation of blood flow and emigration of white cells. Clotting of the blood follows, and this, plus damage to the lining of the vessels which initiates a progressive thickening of the vascular wall, will lead to the occlusion of the vessel. These changes reduce blood flow to the tumour and will in turn affect the growth of the tumour and enhance the direct effects of irradiation on the tumour cells. Systemic factors of a defensive nature have a greater chance to act on the tumour when its growth is slowed down and will in their turn add to the restraining actions on the tumour.

The interaction between vessels and stroma and the tumour parenchyma are very complicated. While bad vascularization may retard the growth of the tumour, it may also decrease the response of the tumour to radiation by lowering the oxygen tension. Hypoxic cells are about three times more resistant to irradiation than well-oxygenated cells. The same effect on the oxygen tension can be brought about by anaemia and local infection —conditions long known to reduce the response to irradiation. Bad vascularization impedes the regeneration of normal tissues and reduces irradiation tolerance. Promising results have been obtained in experimental treatments of patients who are given oxygen while being irradiated, as well as in those treated by certain narcotic agents which reduce the blood flow and oxygen tension in normal regions and increase their tolerance.

Doses of irradiation in the therapeutic range, unlike thermal burns, do not affect all cells of a given tissue alike, even if they are in the same state of activity. Inherent differences in sensitivity of the cells could account for this finding and so could the discrete nature of radiation injury. If, for a lethal effect, the radiation energy has to reach or hit a 'target' in the cell (probably in the chromosomes which are localized in the nucleus), the chance of a hit by the randomly distributed radiation energy will increase with the dose of radiation and the size of the target area. Energy dissipated outside the target area will produce at most an injury which allows the cell to recover. Thus the chance hit of a target in equally sensitive cells can account for the differential effect on cells in irradiated tissues.

The extent to which tumours respond locally to radiation treatment varies with the site in which the tumour arises, with the cell-type of origin, with the degree of anaplasia of the tumour, with its extent and volume and environmental conditions, and the systemic factors in its host. Thus over 90 per cent of keratinizing well-differentiated carcinomas of the skin and lip prove amenable to radiotherapy, while the pigment-forming tumours of the skin (melanomas) are far less susceptible to treatment. Apparently similar types of cancers arising in the cheek, tongue, oesophagus and uterine cervix respond very differently to treatment. The prevalence of anaplastic tumours at some sites accounts for the poor results. The number of viable cells to be killed in anaplastic tumours is far greater than that in differentiating neoplasms of the same volume, since the differentiated, non-viable cells make up a good part of the volume of the latter and the better developed stroma further reduces the viable number. Even with equal radiosensitivity the same dose of radiation would be expected to be more effective in curing tumours with a smaller proportion of reproductive cells. There are, however, also inherent differences in the radiosensitivity of cells, as can be seen from the observation that under well-oxygenated conditions the dose necessary to reduce the growth of cell clones in cultures varies by a factor of almost three.

Originally, embryonic cells, cells of the blood-forming organs, the intestine, the gonads and of anaplastic tumours, were considered particularly sensitive to radiation, because many died quickly after exposure to small doses. It is now realized that this speed of reaction depends on the life span of cells, ie, the intermitotic period of dividing cells rather than on their special sensitivity. In fig. 2, the influence of a rapid turn-over on the changes in the volume of the irradiated tumour is shown, assuming an equal radiosensitivity of stock cells and an equal resorption period for killed cells. In normal tissues, such as the skin, a steady state is achieved by the formation of one new cell for each cell lost from the surface. The intermitotic period is only a fraction of the time taken for the cells to keratinize and be shed from the surface. The killing of potentially dividing cells will be obscured by the presence of differentiated cells until they reach the end of their normal life-span and are not replaced from below. In an anaplastic tumour the volume change will depend only on the short-lived stock cells and thus be revealed quickly, while in the more differentiated tumours an intermediate position obtains between the normal skin and the anaplastic tumour.[4]

Thus speed of reaction is no clear guide to the likely result of radiation treatment, if assessed macroscopically by shrinkage of the tumour. Indeed, increased keratinization is one of the important mechanisms of curing and may prevent shrinkage for some weeks, since these keratinizing cells are initially larger than the potentially dividing cells (figs. 3 and 4). The slow resorption of the hard cornified material may give the impression of the persistence of a tumour which in fact is composed only of sterile cells and rendered harmless. The course taken in the individual tumour cannot be accurately predicted before starting treatment, but the progress under exposure can be checked by histological investigation of samples of the tumour at various intervals during treatment. Thus additional therapeutic procedures such as surgery can be instituted in the case of refractory tumours.[5] Oddly enough, a similar check can be made on normal cells exfoliated from the neighbourhood of the tumour or even from a distant test site. Thus the response to radiotherapy of a carcinoma of the uterine cervix can be assessed by the reaction of exfoliated cells from an irradiated small area in the lining of the cheek.

Thus the tumour and the normal tissue of the host may have the same radiosensitivity and each individual may have his own radiosensitivity which he passes on to the tumour. Against this interpretation is the fact that of multiple tumours coexisting in the same patient (or animal) some may prove refractory and others responsive. In some patients, tumours are composed of two cell strains showing different radiosensitivities in spite of their close proximity. Alternatively, some tumours may be able to decrease the host's radiosensitivity and this would account for the fact that the local response of a tumour tends to be the less the more advanced or wide-spread the tumour is in the body. Here again, the difference in radiosensitivity of multiple tumours and of multiple cell strains in the same tumour are difficult to reconcile with this hypothesis. Perhaps anaemia of the patient is due to the refractory tumour, or alternatively that anaemic patients get the refractory tumour. There is undoubtedly some interaction, probably two-way, between the host and the cancer.

The importance of systemic factors in the control of cancers is revealed by the not infrequent examples of late recurrence of carcinoma. Patients who have lived free of symptoms for five or more years after treatment may succumb to a flare-up of the cancer, often in secondary sites such as bones and lymph nodes. These deposits must have been present at the time the primary was successfully treated; and though the secondary deposits were not, or only insufficiently, irradiated, their growth must have been restrained for these prolonged periods. There are suggestions that endocrine and immunological changes are concerned in this control.

They serve as a vivid reminder that we are dealing with a patient suffering from a neoplastic disease rather than with the destruction of cancerous cells in a human body. The exploration of systemic control, the search for chemical sensitizers, and the use of oxygen in radiotherapy are likely to improve the effectiveness of this form of treatment. But all these new methods must be applied to selected cases. Too often, new techniques are applied to all patients and thus the advantages of the replaced as well as the replacing technique are probably lost. It is essential that the suitability of the technique be assessed by checking the response of the individual patient's carcinoma to treatment, either directly or by checking on the radiosensitivity of the normal tissue. Not only do cancers differ one from the other, but also they are in different environments created by individual patients. Control of cancerous growth by promoting differentiation of cells is as important a factor in the cure of neoplastic diseases as is the destruction of cancerous cells. This aspect has been neglected in chemotherapeutic research.

The greatest promise in dealing with cancers is in early detection of the cancerous changes, possibly at a stage when they are still 'responsive' to some of the regulatory mechanisms and still circumscribed. This is quite feasible for certain sites at least, and a regular check-up on exfoliated cells has proved of enormous value in cancer of the uterus. Many patients with amenable tumours have benefited from early discovery and treatment, which is less extensive and more successful at this stage of the disease.

None of the present therapeutic methods deal with the causative physical, chemical and viral agents. The reduction of the hazardous contacts with some of the agents (cigarette smoking, radiation, etc) may offer some hope of preventing or at least delaying some neoplastic diseases. The development of cancers is also conditioned by the internal environment, and hormones in particular are implicated, as the differential distribution of various cancers in males and females indicates. We need a better understanding of their role in the genesis of tumours.

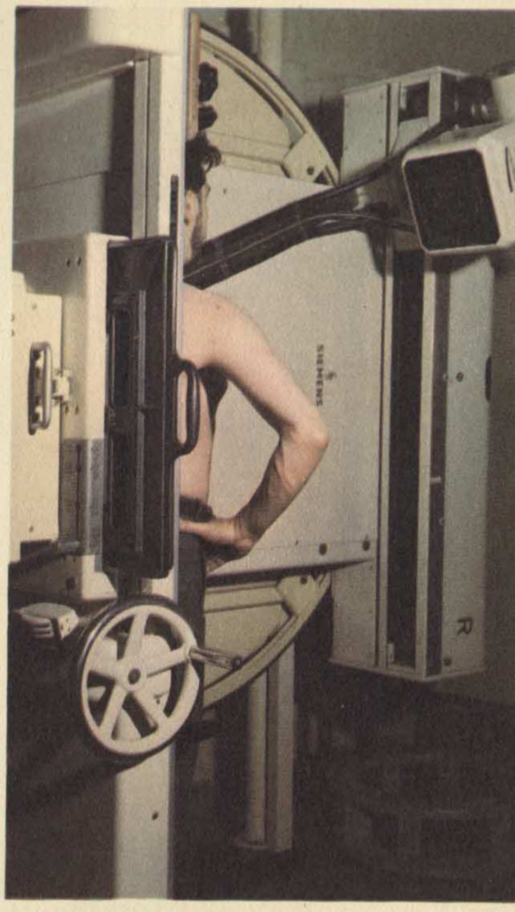


*Fig. 5. Siemens radiotomography equipment. This apparatus makes it possible to take radiographs at different depths in the body of the patient. Comparison between the different radiographic 'sections' obtained in this way make it possible to locate the lesion accurately in space. (Photo Lod, taken at the Centre de Radiographie of the Fondation Curie, Paris.)*

(5) *Curiously enough, it is possible to undertake an analogous test by means of exfoliated cells near the lesion or even in control regions at a distance from it. This is why it is possible to test the reaction to radiation of a carcinoma of the uterine horn by means of the response of cells on the buccal surface of the cheek. It may be that this is a proof of equality of radiosensitivity of tumours and healthy tissues, in which case it would be justified to conclude that each individual has a characteristic coefficient of radiosensitivity that he transmits to the tumour.*

# The treatment of leukaemias

*Georges MATHÉ*

*Not long ago, the only treatment for acute leukaemia consisted of irradiation of the lymphatic organs, the sources of the lineage of the white cell. Today, the uncontrolled and increased proliferation of the white cells in leukaemia can be temporarily arrested for periods lasting from one to five years by such chemical substances as cortisone,* 6-*mercaptopurine and imuran, but we are far from a real cure for leukaemia.*

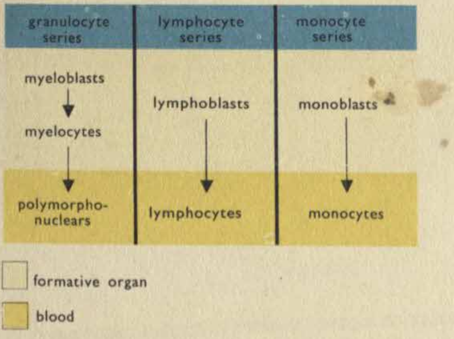


*Fig. 1. Not all white blood cells have the same lineage of cell descent. We can distinguish:* (a) *in the bone marrow, the granulocyte series, which give rise to the polymorphonuclear cells (eosinophils, basophils, and neutrophils);* (b) *the lymphocyte series, the members of which (lymphocytes) are derived from the lymphatic organs (lymph nodes, spleen, tonsils);* (c) *the monocyte series, the cells of which (monocytes) are formed in the bone marrow and the lymphatic organs.*

Leukaemias are malignant neoplastic diseases in which there is a proliferation of both mature and immature leucocytes or white cells.

There are several kinds of leucocytes, of which the three principal groups are the granulocytes, the lymphocytes, and the monocytes. Microscopic examination of the haemopoietic tissues enables us to recognize the stages of differentiation through which these cells pass from their origin until their death. The first group comprises myeloblasts, myelocytes, and polymorphonuclears; the second comprises lymphoblasts and lymphocytes; and the third, monoblasts and monocytes.

Leukaemic proliferation usually involves only one group at a given stage: *(a)* in acute leukaemias there is excessive multiplication of the primordial cells: ie, lymphoblasts in lymphoblastic leukaemia, myeloblasts in myeloblastic leukaemia, monoblasts in monoblastic leukaemia; *(b)* in the chronic leukaemias the cells proliferate at a more advanced stage of their development—lymphocytes in lymphocytic leukaemia; myelocytes in myeloid leukaemia, and monocytes in monocytic leukaemia.

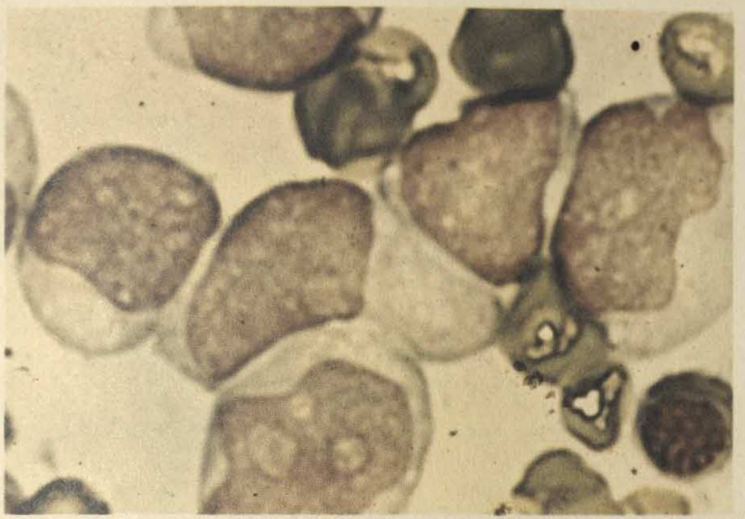
In the normal state, the granulocytes are derived from the bone marrow, the lymphocytes chiefly from the lymph nodes and the spleen, and the monocytes from various organs at the same time. In the foetus, the spleen, which produces the lymphocytes after birth, is the site of origin of the granulocytes and it can become so again in leukaemia.

## *The acute leukaemias*

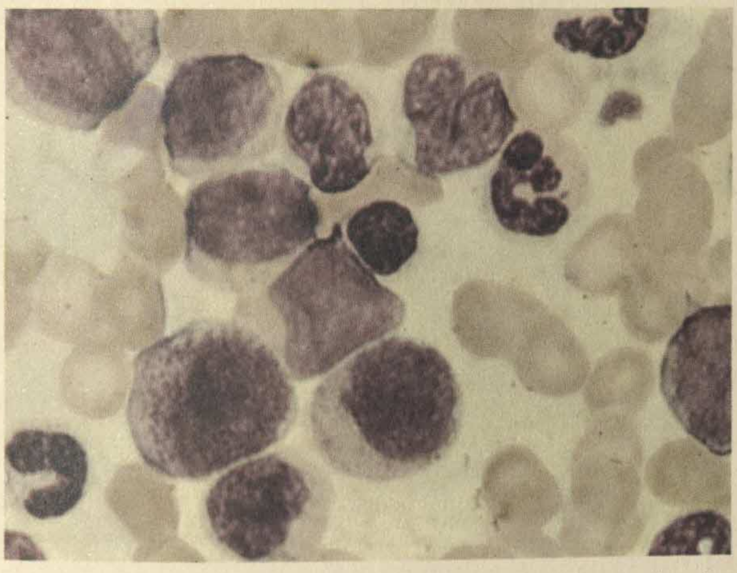
The acute leukaemias may appear at all ages, but the lymphoblastic form predominates during childhood.

The abnormal cells rapidly invade all the haemopoietic tissues, causing neoplastic proliferation of malignant cells and scarcity of normal elements.

This neoplastic proliferation may show itself in a hypertrophy of the lymph glands (adenopathy), or of the spleen (splenomegaly), and by an infiltration of the bone marrow and the bone surrounding it, which causes symptoms of more or less severe epiphyseal pains, osteoporosis, osteolysis, and detachment of the periosteum, all of which can be seen by X-rays. Samples of the blood, bone marrow, lymph-gland tissue and spleen tissue enable one to see lymphoblasts, myeloblasts or monoblasts in smears made for cytological examination, or on sections cut for histological examination. The passage of these cells into the blood is more or less abundant, according to the degree of their proliferation, and perhaps other factors, and the total number of white cells in the blood may be considerably or moderately increased. Sometimes, especially at the beginning of their development, the neoplastic cells do not circulate in the peripheral blood and can only be detected by puncturing the bone marrow. The scarcity of normal elements results in the blood showing

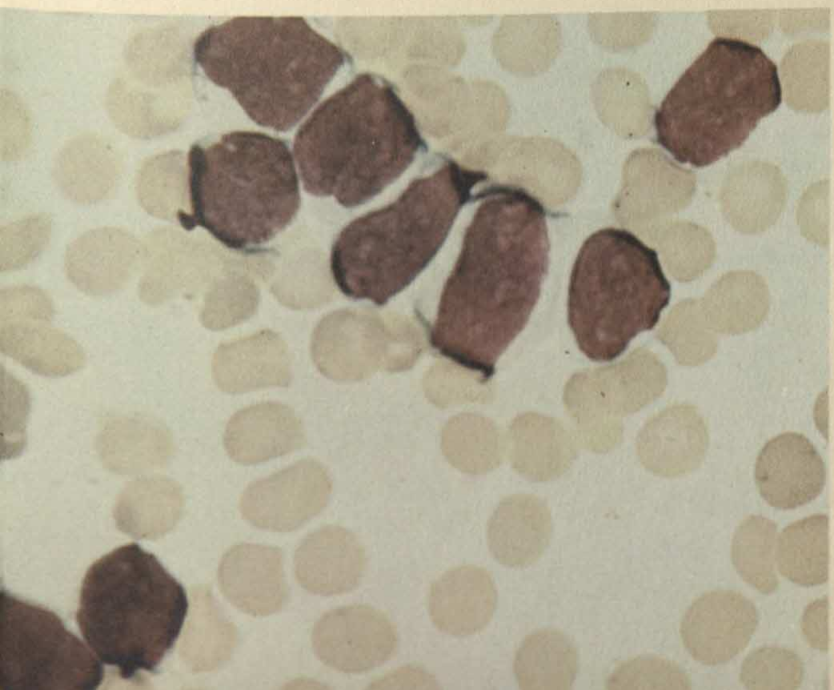


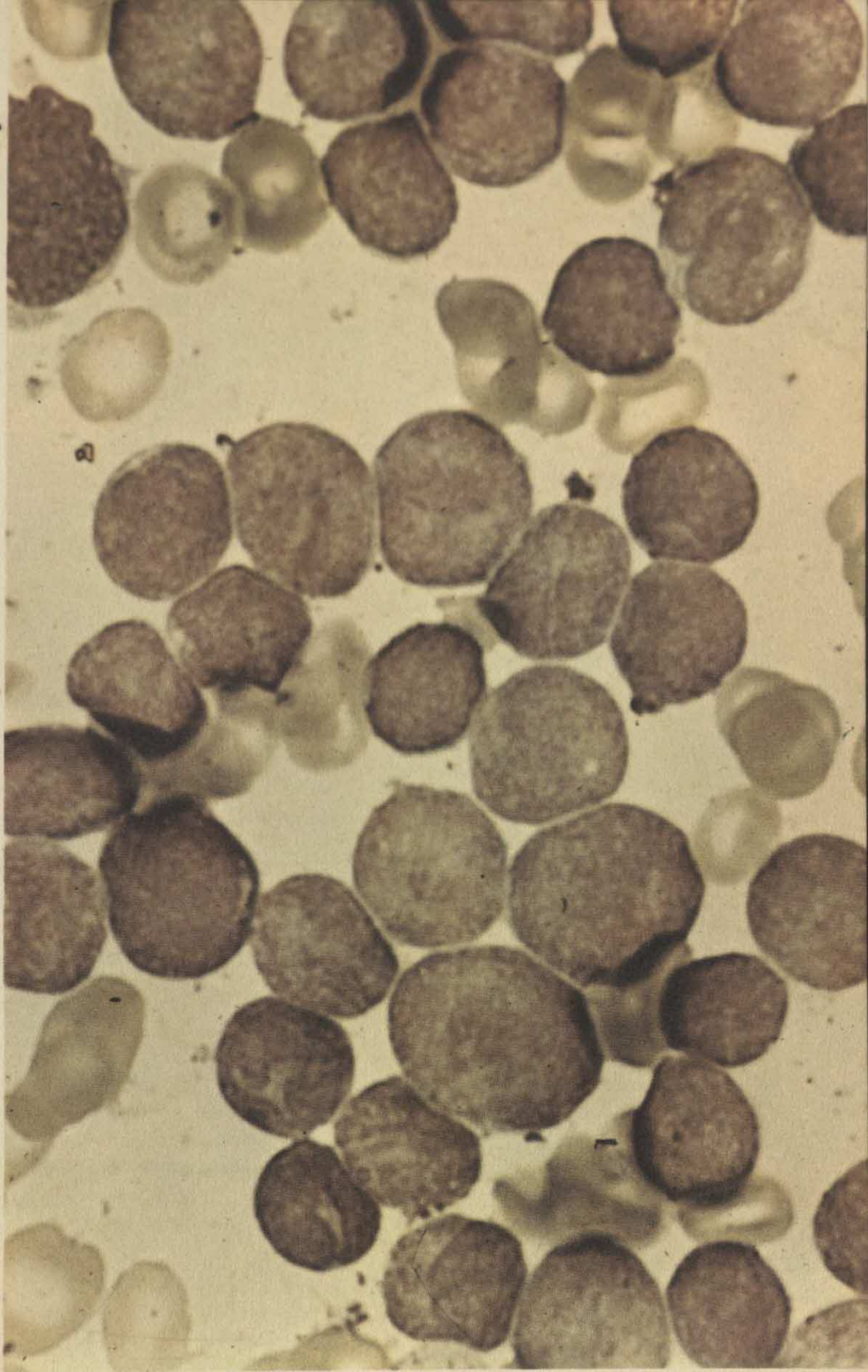
*A smear of bone marrow from a patient suffering from acute monoblastic leukaemia.*



*A smear of the blood of a patient suffering from chronic myeloid leukaemia.*

*A smear of the blood of a patient suffering from chronic lymphoid leukaemia.*





*On the right, from above downwards: a smear of the bone marrow of a patient suffering from leukaemia with promyelocytes.*

*It is by examination of the blood and bone marrow of patients liable to be attacked by leukaemia that excessive proliferation of lymphoblasts, myeloblasts and monoblasts—a clear sign of this terrible disease—is revealed. (Illustrations prepared by Professor Mathé).*

either a decrease in the number of red blood cells or anaemia, which is shown clinically by pallor, or by a decrease in the number of granulocytes (which appears in a tendency to infection) or by a decrease in the blood-platelet count, shown by a tendency to haemorrhages of the skin (purpura) or of the mucosae or viscera.

## *Treatment of acute leukaemias*

Various therapeutic measures can be taken. *Symptomatic* treatment includes blood transfusion to combat anaemia; blood-platelet transfusion to counteract the tendency to haemorrhage due to the lack of these elements; and antibiotics to combat infectious complications which may follow a decrease in the normal number of granulocytes.

Treatment for the *proliferation of cells* is of two kinds: hormonal (ACTH, cortisone and its derivatives) and chemotherapeutic (antimetabolites[1]), of which the most effective are the antifolic drugs, among which those most frequently used are amethopterine and aminopterine (Farber, 1950) and the antipurines, especially 6-mercaptopurine[2] and imuran.

In myeloblastic and monoblastic anaemias the outlook is seldom favourable. In the lymphoblastic leukaemias it is favourable much more frequently. In more than 70 per cent of cases a remission of the disease is obtained. There is either a complete or a partial disappearance of all the clinical and microscopic signs. This situation may last from a few weeks to a year or even longer, but is always followed by a relapse. Several such remissions may follow one another, but they become shorter and less complete each time. Death is inevitable, either because of the intensity or the site of the cellular proliferation; more often it is due to complications connected with the diminution of the number of normal blood cells, such as haemorrhage in the nerve centres and the digestive tract, severe or parasitic infection (thrush).

Attempts have been made to treat the disease by a number of daring methods. By change transfusion of blood (M. Bessis and Jean Bernard) it has been possible temporarily to arrest the initial phase of the disease. The aim of certain researches now in progress is total irradiation, followed by grafts of bone marrow. American medical research teams (especially those of Ferrebee, Atkinson and Kurnick) have induced remissions by radiation treatment of patients in the relapse phase and by injecting them with their own bone marrow; marrow of an identical twin has been used in the case of a twin with the disease.

INCIDENCE OF LEUKAEMIAS IN PATIENTS WHO HAVE BEEN IRRADIATED (AFTER UPTON)

| Approximate dose (in Röntgens) | Therapeutic irradiation (for spondyloarthritis) | Accidental irradiation (Hiroshima) |
|---|---|---|
| 2 250 | 2,068 % | |
| 1 750 | 0,497 | |
| 1 300 | | 1,33 |
| 1 250 | 0,359 | |
| 750 | 0,239 | |
| 500 | | 0,266 |
| 250 | 0,139 | |
| 50 | | 0,032 |
| 5 | | 0,015 |

Our own research is directed towards grafts of homologous marrow (donor and receiver not being identical twins), the only method which makes it possible to cure the disease in animals. So far, we have obtained only temporary arrests of the disease. In man, we have noted a complication of homologous marrow grafts as known in animals, namely, a secondary syndrome (or homologous disease). Experimental research on man is at present directed towards the treatment and prevention of this complication.

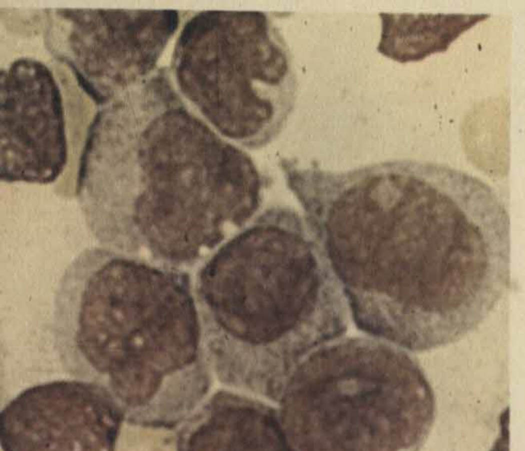


*Fig. 2. A smear of the bone marrow of a patient suffering from lymphoblastic leukaemia. (Photo by Professor Mathé).*

## *Chronic leukaemias*

Chronic *lymphocytic leukaemia* is predominantly an old persons' disease; it does not occur in children. It is caused by excessive proliferation of lymphocytes. In serious cases this causes numerous and voluminous adenopathies, splenomegaly, the formation of nodules, plaques or cutaneous tumours, and various localized enlargements of the tonsils, parotid glands, etc. There is also a considerable increase in lymphocytosis. The disease may also be of moderate intensity, showing itself by an unimportant hypertrophy of some of the lymph glands, a slight increase in the volume of the spleen and the number of circulating lymphocytes. In both cases bone-marrow puncture reveals invasion of the bone marrow by these cells; this invasion, however, will allow a sufficient number of myeloid cells to divide and produce normal blood cells, so that the anaemia remains moderate. Infections

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(1) Antimetabolites: *substances with chemical compositions very near to those of certain metabolites which are indispensable at various levels in the synthesis of nucleic acids: when the antimetabolites substitute themselves for the normal elements, they block nuclear division.*

(2) *For the formula of 6-mercaptopurine, see p. 90.*

(3) Alkylating agents: *substances that have one or several chains of the alkyl series, which are highly 'reactive' and have a strong tendency to combine with certain protein groups, especially nucleoproteins, whose denaturation they thus cause. The nitrogen mustard gases are alkylating agents.*

are rare and the tendency to haemorrhage, if it exists at all, is only a minor danger.

There is, however, a frequent risk of two complications: *(a)* anaemia due to haemolysis (excessive destruction of red blood cells), connected with the production of auto-antibody (an antibody which the patient produces against his own red blood cells); *(b)* serious accidents resulting from smallpox vaccinations, which reveal themselves by local necroses and severe general symptoms; these may be so serious that vaccination should be absolutely forbidden in such patients.

For a long time the treatment of chronic lymphocytic leukaemia was limited to radiotherapy of the neoplastic masses in the lymphatic glands, spleen or elsewhere. But for some years this has been less in favour than chemotherapeutic methods, for which alkylating agents[3] are used, principally an aromatic nitrogen mustard gas, chloroethylamino-phenyl-butyric acid (Galton, 1955) and in addition, ethyleneimine-quinone. Treatment with these drugs makes it possible to effect a notable reduction of the hypertrophy of the haemopoietic organs and the lymphocytosis in the blood within a few weeks, following which the disease may be held in check for several years. Relapses and remissions follow each other, as they do in acute leukaemias, but the total duration of the disease is, on the average, five or six years and may even exceed ten. Death may be due to a particular location of the tumour, to a complication (haemolytic anaemia), or to insufficiency of the normal functions of the bone marrow, owing to infections or haemorrhages.

*Chronic myeloid* leukaemia, though it may occur at any age, predominates in adults. The abnormal proliferation essentially affects the neutrophil granulocytes; it considerably increases the number of myelocytes and the cells in a more advanced stage of development (metamyelocytes). It may also affect the two other sub-groups, the eosinophils and the basophils.

This proliferation is located chiefly in the bone marrow (seat of the formation of the granulocytes after birth) and in the spleen (seat of their normal formation during foetal life). The two principal symptoms of the disease are pains in the bones, usually not very severe, and hypertrophy of the spleen (splenomegaly): the spleen is often greatly enlarged. The number of immature granulocytes in the peripheral blood is usually considerable and as a result leucocytosis is very much increased. The proliferation of these cells can be seen in smears of the medullary and splenic tissues sampled by puncture.

The disease is usually well tolerated for three to five years: treatment of the first phases is by local radiotherapy applied to the spleen or by chemotherapy, chiefly dimethane-sulphonyl-oxybutane (Galton, 1955) and de-acetyl-methyl-colchicine or the derivatives of ethylene-imine-quinone, which brings the size of the spleen back to normal and reduces the hyperleucytosis, allowing excellent chances for temporary remission of this disease.

While the disease advances, relapses are repeated and remissions from it become shorter and less complete. The proliferation, which affects the leucocytes, which are immature but differentiated in the direction of granulocytes, gives place to proliferation of the primordial cell, as if the chronic leukaemia had disappeared and given place to an acute leukaemia. Whether this indicates a modification in the site of attack of the agent that causes leukaemia or a succession of two different leukaemias, it is not possible to say, but this 'acute transformation' has no equivalent in chronic lymphocytic leukaemia.

The patient is attacked from that moment by a disease of which the picture and development are no different from those of leukaemias that are acute from the beginning. *Chronic monocytic leukaemias* are rarer than those we have already discussed and may attack people of all ages. Associated with a malignant proliferation of the monocytes and the tissue cells which generate them (the histiocytes, which are mobile, and the reticular cells, which are fixed), these leukaemias usually cause hypertrophy of the spleen and lymphatic glands. In the peripheral circulation there is a variable but often moderate increase in the number of monocytes and in leucocytosis.

Treatment, according to the manifestations of the disease, may include administration of adreno-cortical hormones of 6-mercaptopurine, of an alkylating agent, or of vinblastine or vincristine (alkaloid extracts of the water-periwinkle). The course of the disease extends from one to five years.

Thanks to the discovery of a number of chemical substances which prevent the excessive proliferation of the cells belonging to the white blood-cell lineages (both the primordial cells and the differentiated cells), the prognosis of the leukaemias, whether they are acute or chronic, is no longer as sombre as it was ten years ago; but a remission of the disease does not signify a cure and the problem of leukaemia remains one of the gravest in medical research.

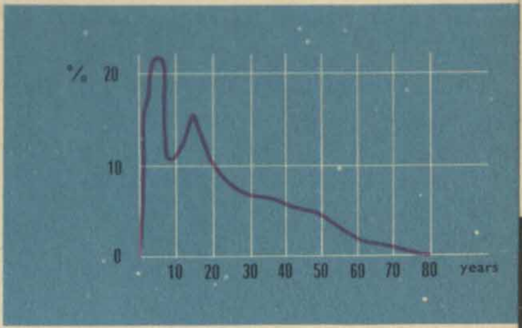


*Fig. 3. Frequency of acute leukaemias according to age. Note the two summits of the curve, one about five to six years, the other about fifteen years.*

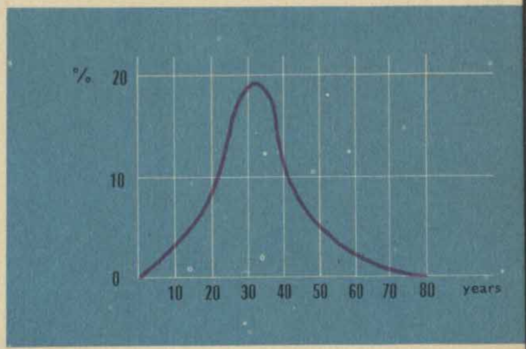


*Fig. 4. Frequency of chronic lymphocytic leukaemias according to age. The difference between this curve and the preceding one will be noted.*

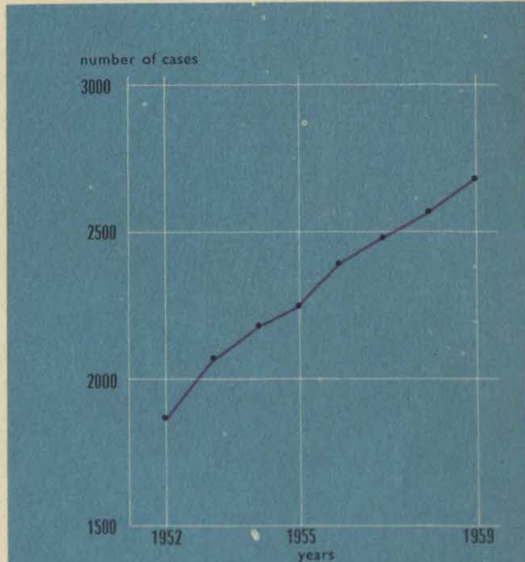
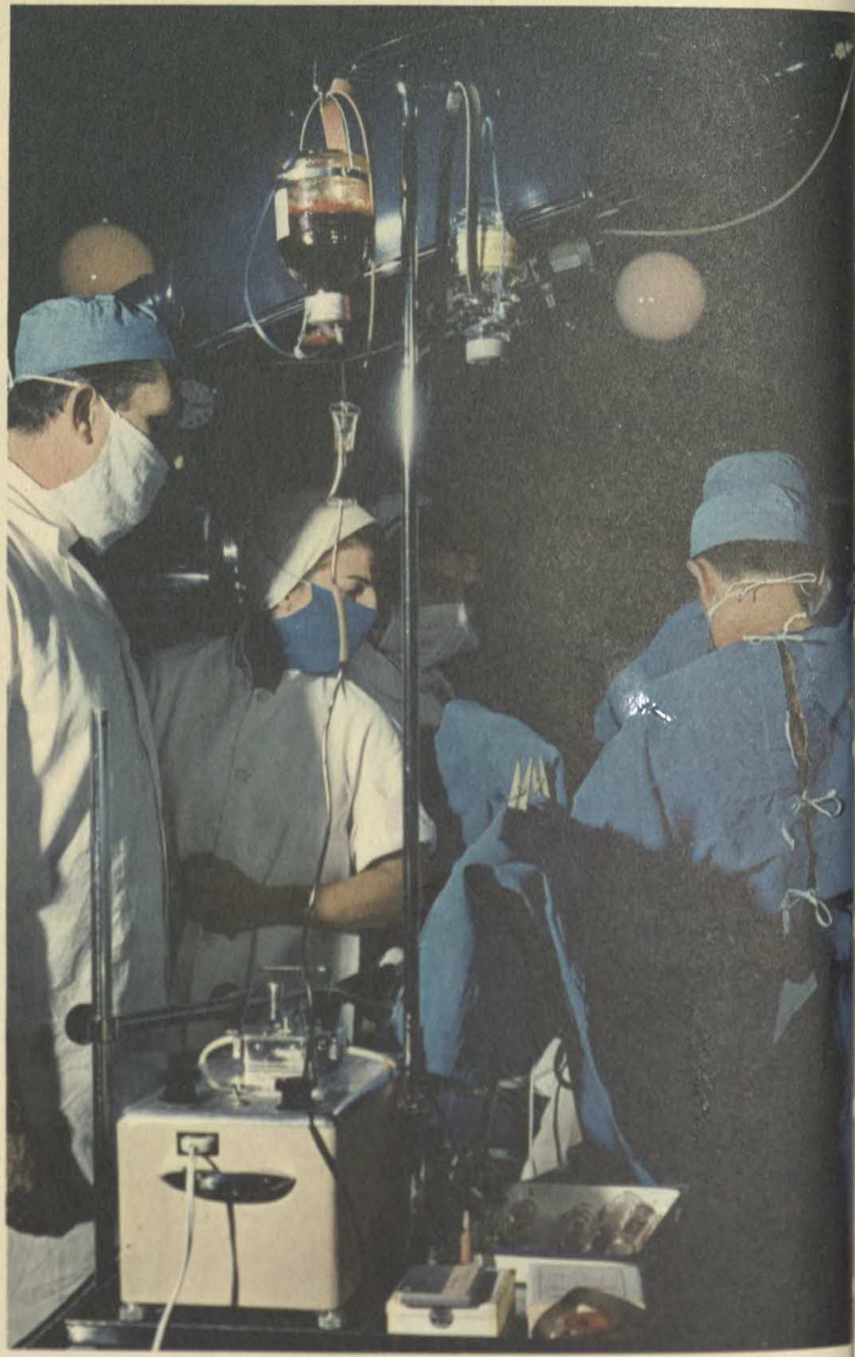


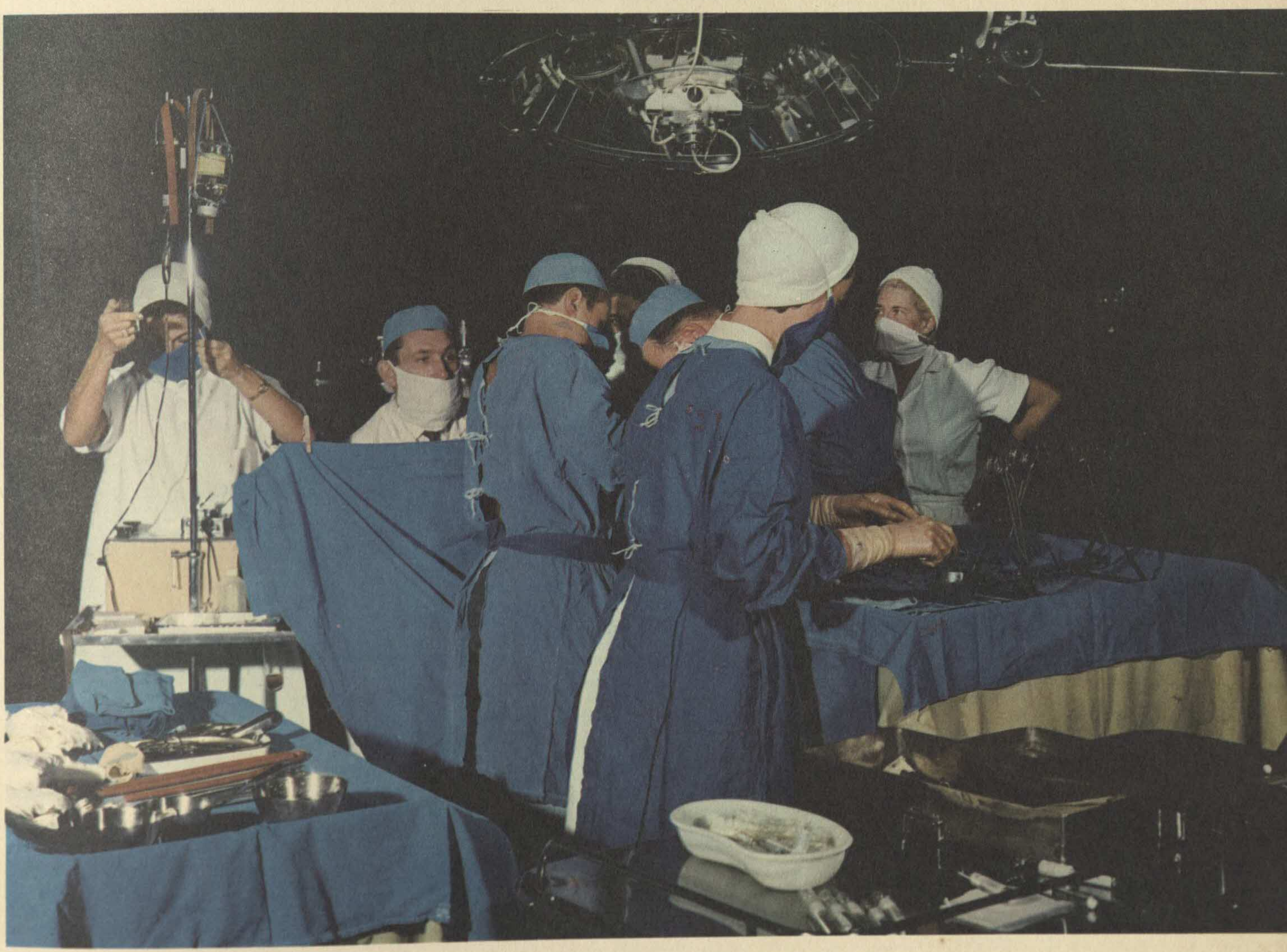
*Fig. 5. Increase in the number of cases of leukaemia in France between 1952 and 1959.*

# PART FOUR



*Modern surgery has become a job of team-work. Under the direction of the surgeon—conductor of the orchestra, as it were—the anaesthetist, male and female nurses, assistants, and others in charge of instruments and apparatus, perform specific duties and control the apparatus which makes it possible to operate with the maximum of effect. Thanks to improvements in the techniques of anaesthesia and resuscitation, the surgeon, without risk or precipitate action, can estimate the relative*

# *The world of surgery*



*significance of the lesions, decide on the surgical technique to be adopted, and allow himself whatever risks may be necessary in excisions, in restoration of physiological conditions, and in sutures. Operations can now last without inconvenience for six to eight hours, whereas only fifteen years ago the same operations had to be performed as quickly as possible. The most spectacular example of this improvement is in cardiac surgery: hypothermia and the artificial heart-lung have made it possible to operate on the exposed heart. Multiple controls (electro-encephalography, intra-arterial pressure readings, pre-operative radiography) mean that the surgeon is no longer merely an expert technician but also an engineer. (Photos Lod, taken in Professor Daumet's operating theatre at the Hôpital Saint-Joseph, Paris).*

# Ablative surgery

### *Jean GOSSET*

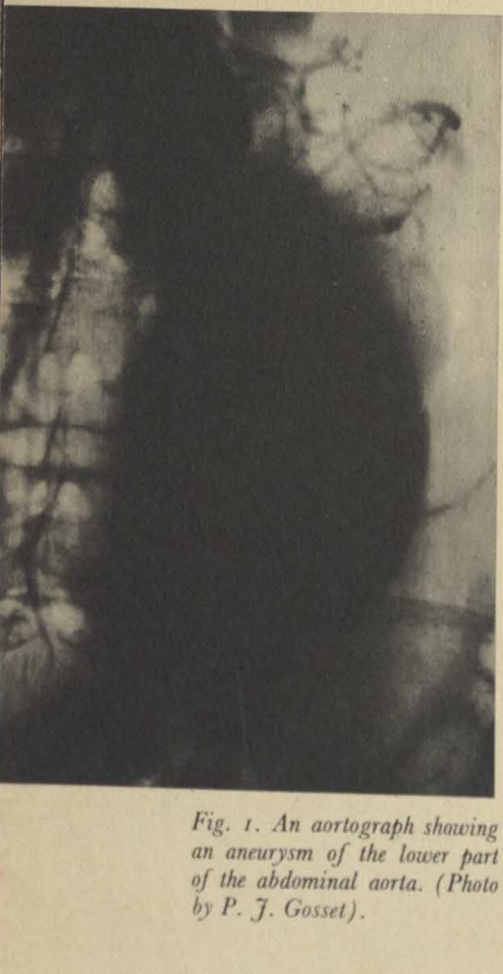


*Fig. 1. An aortograph showing an aneurysm of the lower part of the abdominal aorta. (Photo by P. J. Gosset).*

The field of ablative surgery is so extensive that it would be quite impossible to enumerate all the operations which it includes. Let us therefore try only to classify them.

First, the removal of foreign bodies, both exogenous and endogenous. Exogenous foreign bodies are those which have penetrated an organism as the result of an accident or a wound; endogenous foreign bodies are produced by the organism itself; if left untreated they may become a source of painful or infectious conditions, such as calculi, for example, or concretions, which may be situated in the salivary, urinary, or bile ducts or in the intestine. Often it is impossible, as well as undesirable, to limit an operation to removal of, say, gallstones. It may be necessary to remove the whole organ containing calculi because it may be damaged or its persistence may expose the patient to recurrent gallstones.

It may also be necessary to remove organs or parts that have become necrotic (ischaemic or gangrenous limbs). Again, organs that have been severely injured when an exposed or closed wound occurs must be removed if the organs cannot be repaired. This is often necessary in the case of the spleen, the kidney, or a segment of the intestine.

Organs or tissues which are the seats of infection whose propagation or diffusion threatens the organism must also be removed, as in the case of acute appendicitis, or, for instance, chronic infections such as tuberculosis. A micro-organism, *Staphylococcus* for example, can cause either acute or chronic lesions, such as osteomyelitis, which may make excision necessary.

Abnormal structures of congenital origin (Meckel's diverticulum, cervical rib, etc), or fragments of displaced tissues (disc hernia) often need to be removed. Many tissues suffer from aggressive damage, and if these tissues are not essential, the simplest treatment is to excise them. One can, for example, excise superficial dilated veins or the dense fibrous tissue that characterizes Dupuytren's contracture, or again, chronic ulcers involving the stomach or the duodenum.

Finally, there are the various tumours, benign or malignant, which account for most ablative operations. The surgeon's problems differ according to whether the tumour is benign or malignant. A benign tumour is a localized lesion which is non-recurrent once it has been completely removed. The excision is sometimes restricted to the tumour itself (myomectomy of a uterine fibroma, for instance) but sometimes the excision is more extensive; such an extension is made necessary only on anatomical or physiological grounds, not for pathological reasons.

Cancerous lesions are quite different. Except at the start, cancer is not limited to the organ where it first occurs. Malignant cells migrate into adjacent tissues (local invasion), or into the lymphatic nodes of the diseased area (lymphatic metastases) and often into other organs some distance away from the original lesion (visceral metastases).

The removal of a cancerous lesion therefore always involves extensive excision to eradicate completely not only the tumour but all adjacent tissues and cancerous areas which might be the seat of metastases.

Sometimes it is possible to remove the cause of the trouble completely by this means, and the patient is then cured. But sometimes the malignant cells have extended so far that it is impossible to operate; a recurrence is then inevitable, unless the metastases can be checked by non-surgical means (radiation therapy, radium therapy, and cobalt therapy).

Another form of surgery is that which aims at correcting functional disorders, as, for example, by the removal of certain hormone-secreting glands (suprarenal, parathyroid, pancreas), or certain pathways of the sympathetic nervous system, in order to reduce the effects of excessive glandular secretion or abnormal nervous stimuli. The surgery of arteritis, for instance, aims at causing dilation of the vessels, as much by blocking the sympathetic nerves as by reducing adrenaline secretion which is the main vasoconstrictor agent.

Section of the vagus nerves results in a considerable reduction of the acidity of the stomach, and as excessive secretion of acid seems to be an important cause of gastric ulcers, the severing of these nerves is an effective way of curing them.

In certain instances, removal of a lesion which is of secondary importance is done with only a physiological end in view. Resection of an obliterated artery (arteriectomy) is not just a question of removing a useless vessel. Through the damage which it has undergone the artery may cause harmful excitations and its removal then becomes necessary to suppress them.

Physiological surgery of this kind is, however, often deceptive. Physiological mechanisms, whether endocrinal or nervous, are too complex and too subtle for an act as crude as the use of a scalpel to be unfailingly successful and, above all, durable. Often, after what may appear to be spectacular results, a pathological disturbance will re-establish itself in other ways.

## *Rules and techniques*

All techniques of ablative surgery are based on anatomy. It is this which determines the route of access, the freeing of the lesion, the control of haemorrhage, and the reparatory measures. Usually, the diagnosis will have made it possible for the site of the lesion to be indicated precisely. During preliminary discussions, the type of operative procedure is decided upon, a forecast having been made of the variants that may have to be adopted, based on the exact nature of the lesions. The route of access having been chosen with scrupulous care, the aim must be to mutilate the patient as little as possible, yet to ensure that the incision is large enough to allow easy manipulations. It must be possible for the incision to be enlarged, if necessary, this being done by using the interstices between the muscles, the planes of cleavage which anatomy reveals. Sometimes, if accessory vascular or nerve structures are found to be in the way, these may be sacrificed.

On the other hand, the proximity of a nerve or an organ may sometimes be a danger, especially if one of them should be accidentally injured. Whenever there is a possibility of this happening, there is a strict rule: do not look for a way round the difficulty; go straight to the point of danger, define it accurately, isolate it, and then protect it. This must always be done, for instance, to protect the radial nerve in surgery of the arm, the facial nerve in surgery of the parotid, and above all, the ureter in surgery of the kidney pelvis.

In present-day surgery certain routes of access which used to be dreaded and consequently rejected as being likely to involve too grave a risk, are favoured because they simplify subsequent procedures. This is so with the thoracic and abdomino-thoracic routes. Before modern advances in anaesthesia, surgeons were reluctant to open the pleura. Today, no danger is involved by this operation which, for instance in total gastrectomies, makes possible a more extensive access route and safer and more exact manipulation. The old-fashioned abdominal incision gave only limited freedom and deep manipulations were difficult and therefore dangerous. Today it is possible to perform widely extended ablation with much less risk.

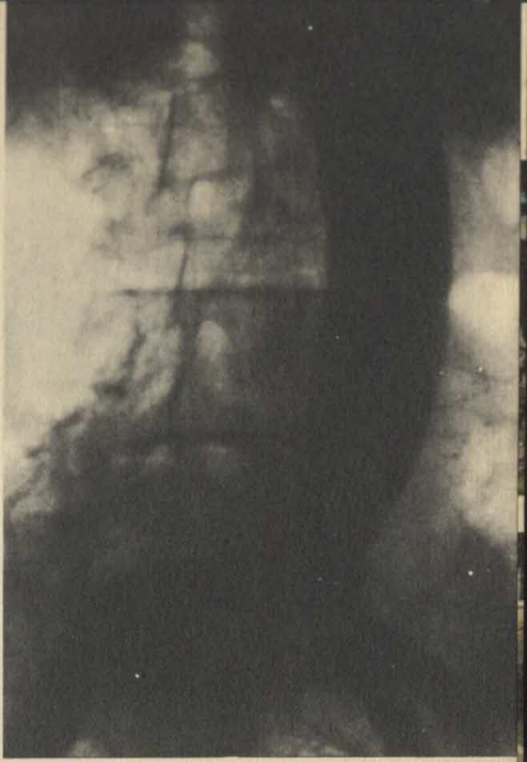
Conversely, in operating for a slipped disc (herniation of the intervertebral disc), at the cost of making a very small incision and of the additional difficulty of working between the contiguous vertebral laminae, the effects of the operation on the vertebral equilibrium, which is highly delicate and easily upset, are reduced.

These two examples have been chosen to show that progress in surgery has different and sometimes even opposite requirements, and that during the operation itself, manual dexterity is less important than reasoning and rational choice.

Anatomy not only guides the surgeon in his route of access, it also determines the rules of ablation. Sometimes this is limited to the lesion itself, sometimes it may be necessary to remove a part or even the whole of an organ.

Ablation involves freeing and separating structures, dissecting, and tissue section. In separating tissues one should always make use of the spaces least likely to bleed and those that are the loosest. These spaces are the cellular areas, the regions joined together in embryonic development, which are called the *planes of cleavage*. Vascular pedicles are divided, but it is necessary first to locate and ligature them. Here also anatomy guides the surgeon, but only when the lesion has not completely disrupted the normal anatomy.

It might seem that when this has occurred the ablative technique should be modified to meet the particular needs of the situation. This is what surgeons with more of the



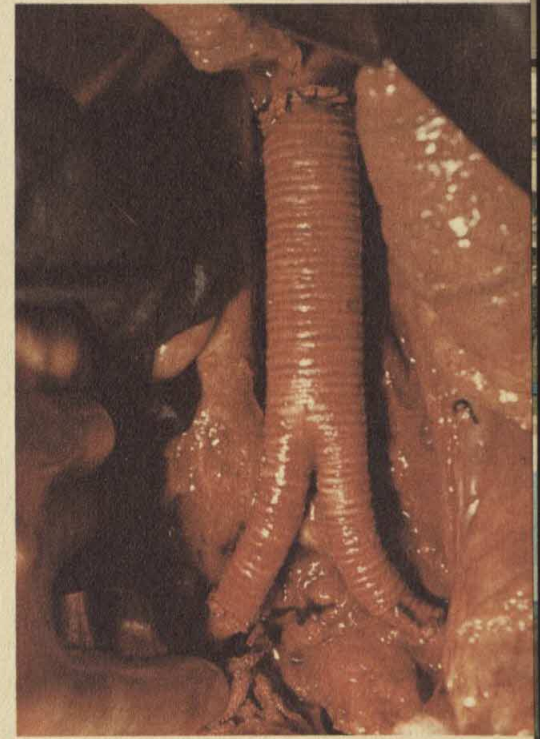
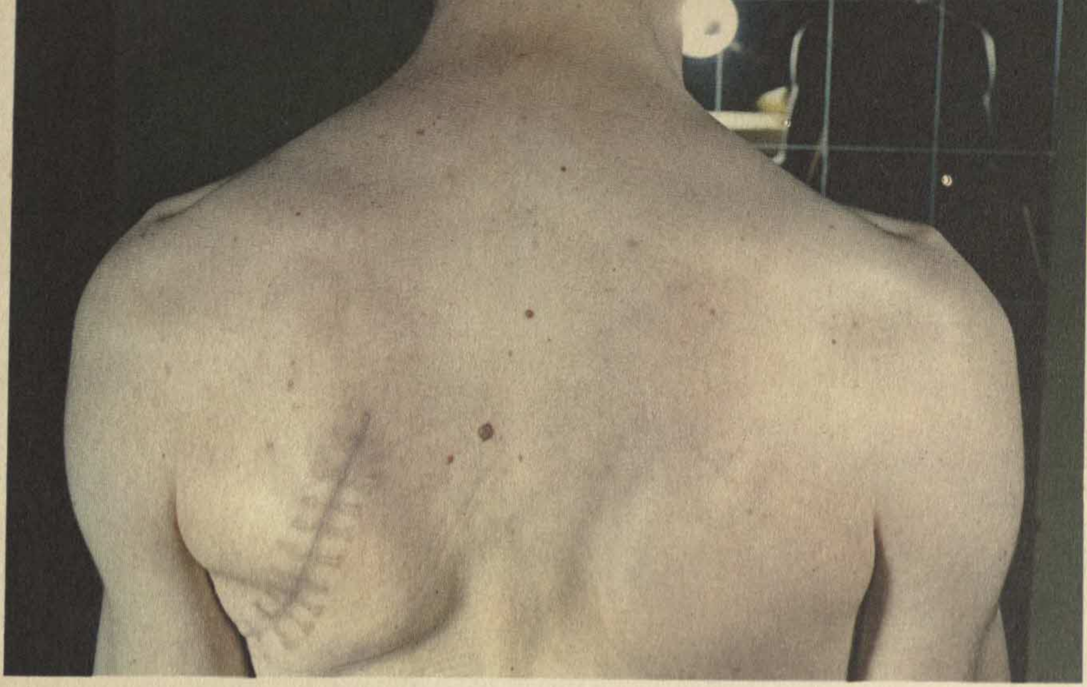


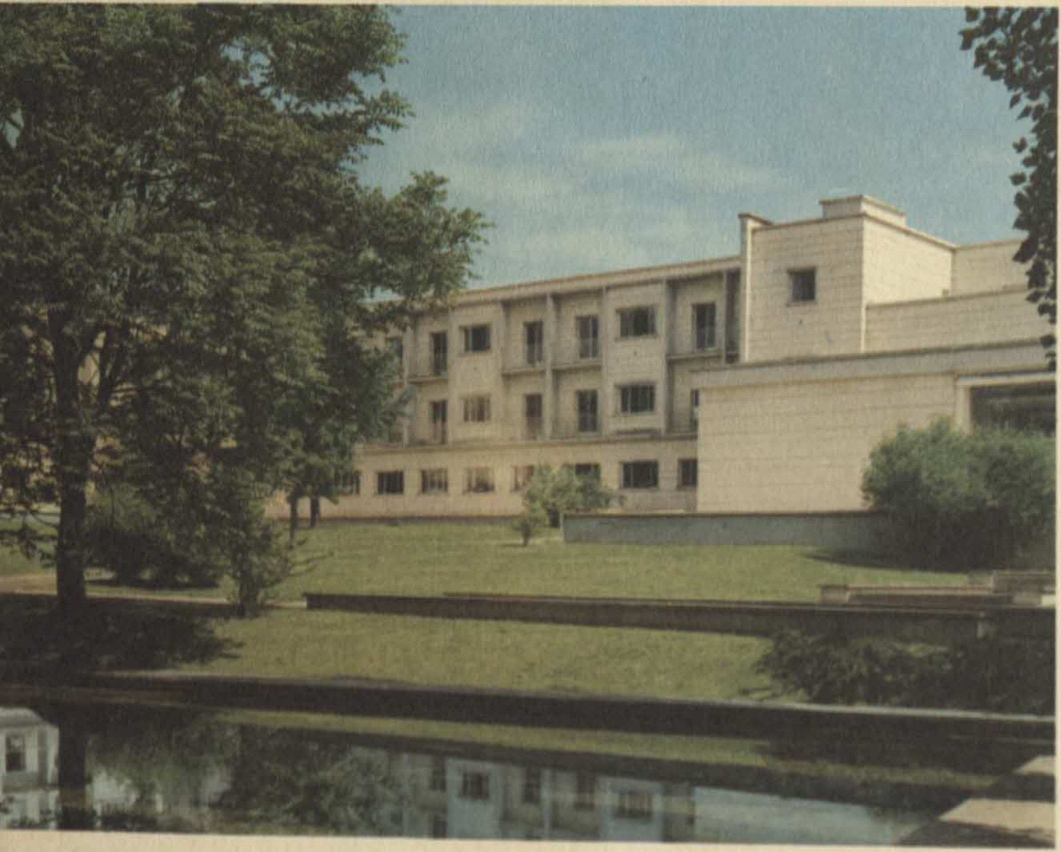
*Fig. 2. Above, an aortograph of the same patient, taken after surgical operation. (Photo by P. J. Gosset.) Below, a photograph taken during the operation: the defective aorta has been replaced by an artery made of knitted dacron, which is immediately colonised by the cells of the vascular wall. (Photo by Dr M. Hivet, Assistant Surgeon at the Hôpital Saint-Antoine, Paris).*


b

## *Post-operative recovery*

*Thoracic surgery is now much to the fore and plays a considerable part in a number of cardio-respiratory operations; in particular, it makes it possible to cure pulmonary tuberculosis. But the former patient recuperating from a major operation often feels that he has become enfeebled and badly adapted to the rhythm of modern life. The period of recuperation will be happier for him if it can be made under conditions such as those in this French convalescent centre at Maisons-Lafitte (a).*

*Functional re-education aims at compensating for the anatomical osteomuscular disorders created by the operation, especially through improvements in the undamaged musculature. Thoracic surgery leaves the patient's general condition impaired; the long scar (b) hinders respiratory movement (Photos Lod).*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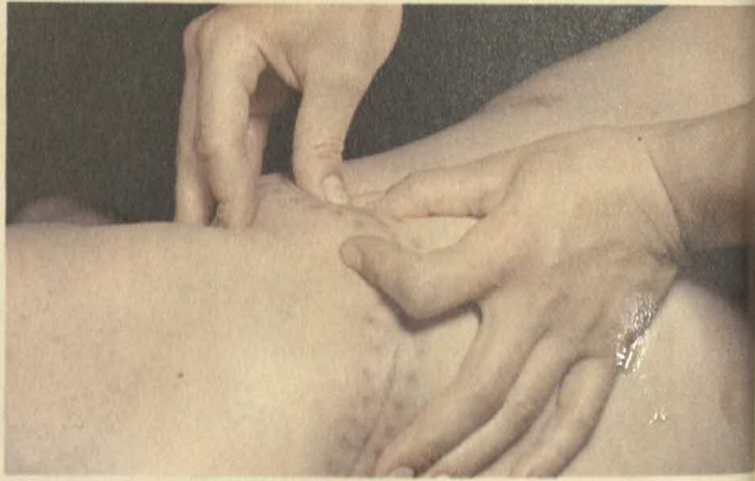
*(c) Massage plays an important part by soothing pain and reducing skin adhesions. Respiratory re-education begins with separate movements of the diaphragm. (d) After the patient has grown accustomed to this exercise, the vigour of the muscle can be increased by giving it resistance to overcome, such as the weight of sand-bags placed on the abdomen. (e) Later on, the use of a belt enables the patient to exercise alone. (f) The exercises are also concerned with the action of the ribs. In the localised expansion of the lower ribs the therapist's hand applies resistance. (g) Some of the pleural symphyses may benefit from electro-gymnastics and corrective and muscular exercises. (i) Re-education of the cervical vertebral column is greatly helped by the use of weights hanging from a band fixed round a crash-helmet, which give effective work to the muscles of the neck. (h and j) Pulleys are used to re-educate the shoulder and the thoracic muscle masses. The aim of physical re-training is to restore the body to its proper physical condition after it has been inactive for a long time. Rhythmical exercises alternate with learning to run again for short distances. Volley-ball has been introduced as a means of psychological relaxation rather than re-education. (k, l, m and n) By progressive exercises adapted to each patient, those who have been cured by an operation will be able to resume their professional and social life without too violent a transition.*

c



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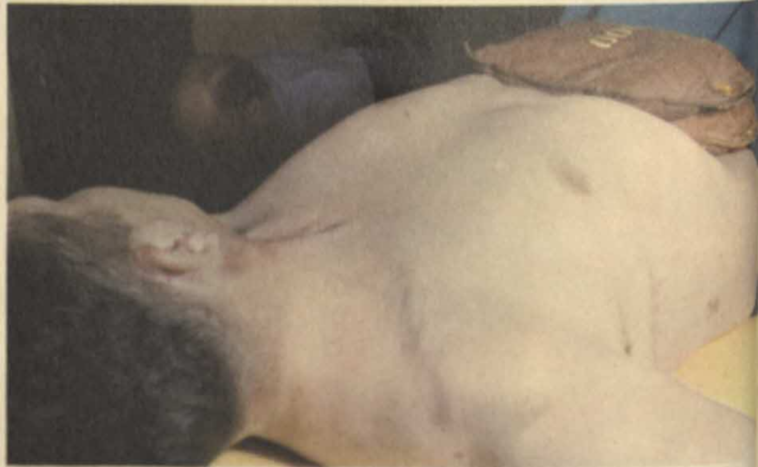

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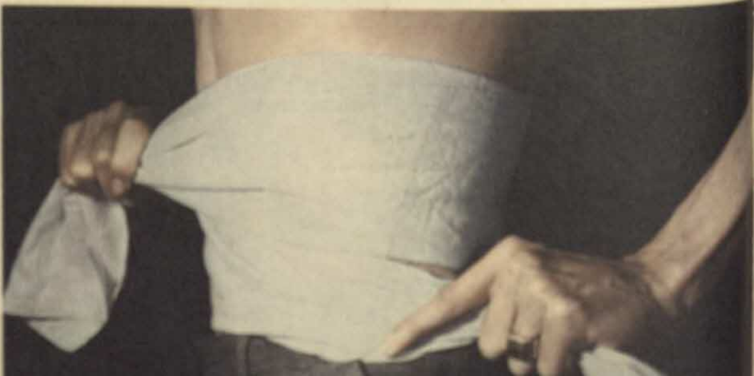

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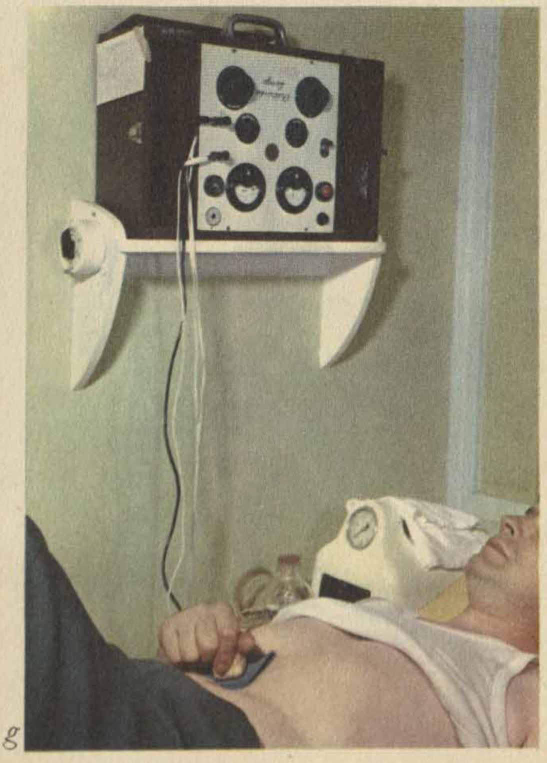
*h*

*i*



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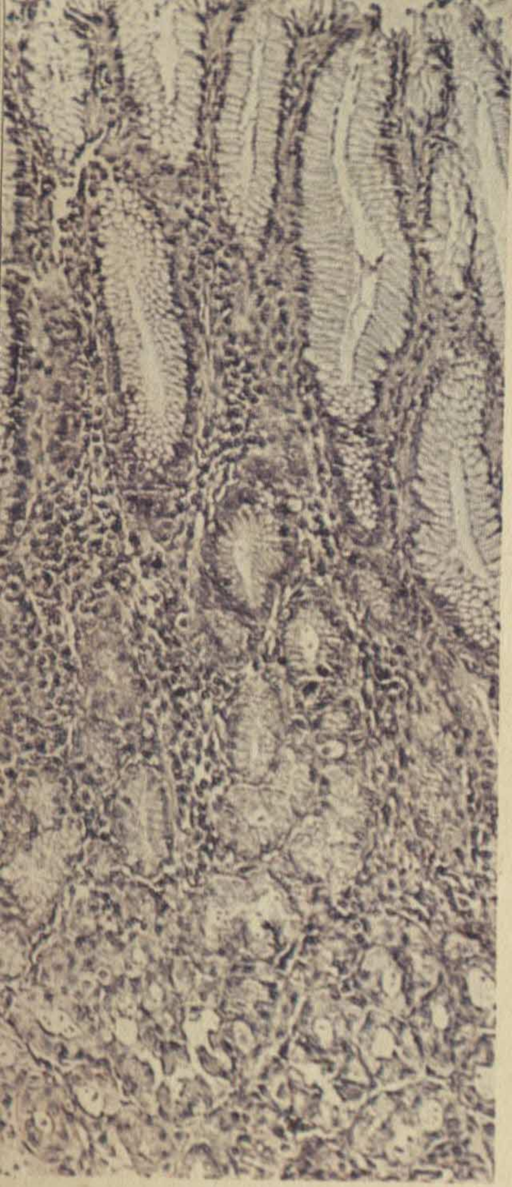

Fig. 3. *Excision is still one of the only techniques that can be used for certain tumours, such as cancer of the stomach. This histological section shows a cancerous infiltration of the stomach-wall beneath the mucosa, which is itself normal. (Photo Lod).*

'surgical touch' than of method or wisdom will usually choose to do. But in such circumstances this is quite wrong: ablation should be divided into two distinct periods, the first devoted to removing what the lesion has created—namely, the adhesions which have disorganized the anatomy—in short, to re-establishing the normal form of the anatomy. This order of procedure makes it possible in most cases to use the classical standardized technique during the second period.

## *The progress of ablative surgery*

The possibilities of ablative surgery used to be limited by the risk to the patient's life and the body's inability to endure certain operative procedures. Many excisions are still impossible because, for anatomical or physiological reasons, they would be fatal. Some tumours, for instance, cannot be removed for this reason. Such are the enormous mesenteric tumours which cannot be removed without sacrificing the blood supply to the small intestine.

Nevertheless, the field of ablative surgery is continually being extended. Serious operations which used to seem reckless, even reprehensible feats of virtuosity, have become common. Why is this? Are the surgeons more daring? Surely not. Though one used to speak of 'courageous' surgeons, it was, in fact, the patients who were courageous in entrusting themselves to the surgeons. Certainly they were the pioneers, and for this they deserve respect. But how many patients have been sacrificed on the altar of surgery, compared with the small successes achieved?

It is not that surgery has perfected itself: it is that its possibilities have been transformed by the parasurgical methods of anaesthesia and resuscitation before, during, and after the operation—methods which are founded on physiology, physics, chemistry, and pharmacology. By making surgery more benign and reducing to a minimum the disorders that are arbitrarily grouped under the name *operative shock*, these methods make it possible to perform, with comparatively little risk, operations which only a short time ago seemed either impossible or highly inadvisable.

The first necessity was to understand what operative shock was, what causes combined, during a major operation, to culminate in fatal physiological disorders. Astonishing though it may seem, surgeons and physiologists for long erred in ascribing undue importance to complex but secondary factors, while neglecting more simple causes the evidence for which now seems so clear that it is difficult to imagine how it could possibly have been overlooked.

The old and most commonly used method of anaesthesia was by inhalation, which was harmless as long as it was only applied for a short time. However quick and dexterous the surgeon was (and speed and dexterity were then indispensable, though they now count almost as defects), he could not perform operations involving long and thorough repairs.

Anaesthesia given in high doses had two effects, the one toxic, the other characterized by depression of the activity of the cerebral, respiratory, and circulatory centres. With the primitive anaesthetic apparatus used, the patient absorbed less and less oxygen, and hypoxia or anoxia were the cause of most failures.

Local and cerebro-spinal anaesthesia had neither of these drawbacks, but their use was limited, either because the muscular relaxation produced was insufficient or because their effects did not last long enough.

Nowadays, deep, general anaesthesia can last as long as four or five hours, sometimes even longer, and can be applied without danger because the anaesthetist's most important concern is to ensure perfect oxygenation of the patient throughout the whole operation. This is now possible because of improvements in anaesthetic apparatus. Whereas the same anaesthetic, either chloroform or ether was used to induce analgesia[1] and muscle relaxation[2] simultaneously, different substances are nowadays combined in variable proportions, some with an analgesic action and others which relax the muscles (natural or synthetic curare). Both anaesthesia and analgesia can now be so precisely controlled at their lower threshold limits as to reduce toxic or depressant effects. Improved knowledge of the physiology of respiration and the continual discovery of new anaesthetics with different properties are the basis of the great change in modern anaesthesia: namely, that it has become harmless. Toxic and nervous factors had been suggested as causes of operative shock. Perhaps they may be, but, if so, only in a secondary way.

Anaesthesia is no longer dangerous in itself, so what is the major danger in ablative surgery? It is the loss of blood by haemorrhage. Although this fact now seems obvious, for a long time it was hidden or neglected. As soon

(1) Analgesia: *the absence of feeling of pain.*

(2) *Relaxation of the muscles, which is essential for the carrying out of surgical operations.*

(3) *A few examples show the diversity of these problems: a salivary calculus or a bladder calculus only require removal. On the other hand, simple ablation of calculi in the gall-bladder, the site of the initial lesion, gives unsatisfactory results. It is therefore necessary*

Continued on page 110

as even a small artery is cut, it is instantly ligatured. But cut surfaces cause blood to seep, and until the simple idea occurred of measuring these seepings, their volume was thought to be negligible. But loss of three drops of blood per second (8 cc per minute) amounts to a loss of a litre and a half during an operation lasting three hours. In spite of the careful arrest of haemorrhage, such losses by seepage are almost inevitable in many major operations, and it is in this that fatal shock originates, especially if, besides loss of blood, there is deficient oxygenation through anaesthesia.

Operative shock has practically disappeared, now that massive transfusions are given at the same time as the operation to compensate exactly for the loss of blood.

## *The risks of ablative surgery*

However safe ablative surgery may be today, all surgery involves a functional risk as well as a risk to life. To what extent must the extent of an ablation be governed by the risk, and by comparison of the risks involved in different methods of excision with the risk arising from the existence of the lesion? This is an essential point and the problems which it raises are infinitely varied, according to the type and nature of the lesion and the organ affected.[3]

Is a lesion always sufficient to justify an operation? The answer is obviously 'no'. If surgery were deprived of all risks, it could no doubt be defended on the principle of systematic ablation of every pathological lesion. But this is not the case. There are lesions whose existence involves less risk than their removal, even when the ablation would be benign. In such cases the decision whether to operate or not must be weighed with care.

The surgeon is often presented with three possibilities: reasoned abstention, radical excision, and limited or conservative excision. It is in this last direction that certain operations have recently shown the most progress. Partial excision of a kidney or of a lobe of the lung would formerly have seemed technically impossible; the only conceivable alternatives would have been a nephrectomy or a lobectomy. Now, thanks to the progress of anatomical studies, it is possible to devise and perform conservative segmental resections in both the lung and the kidney. Arterial blood supply irrigates certain segments of an organ separately and their excision can be effected without damage to the circulation in the rest of the organ.

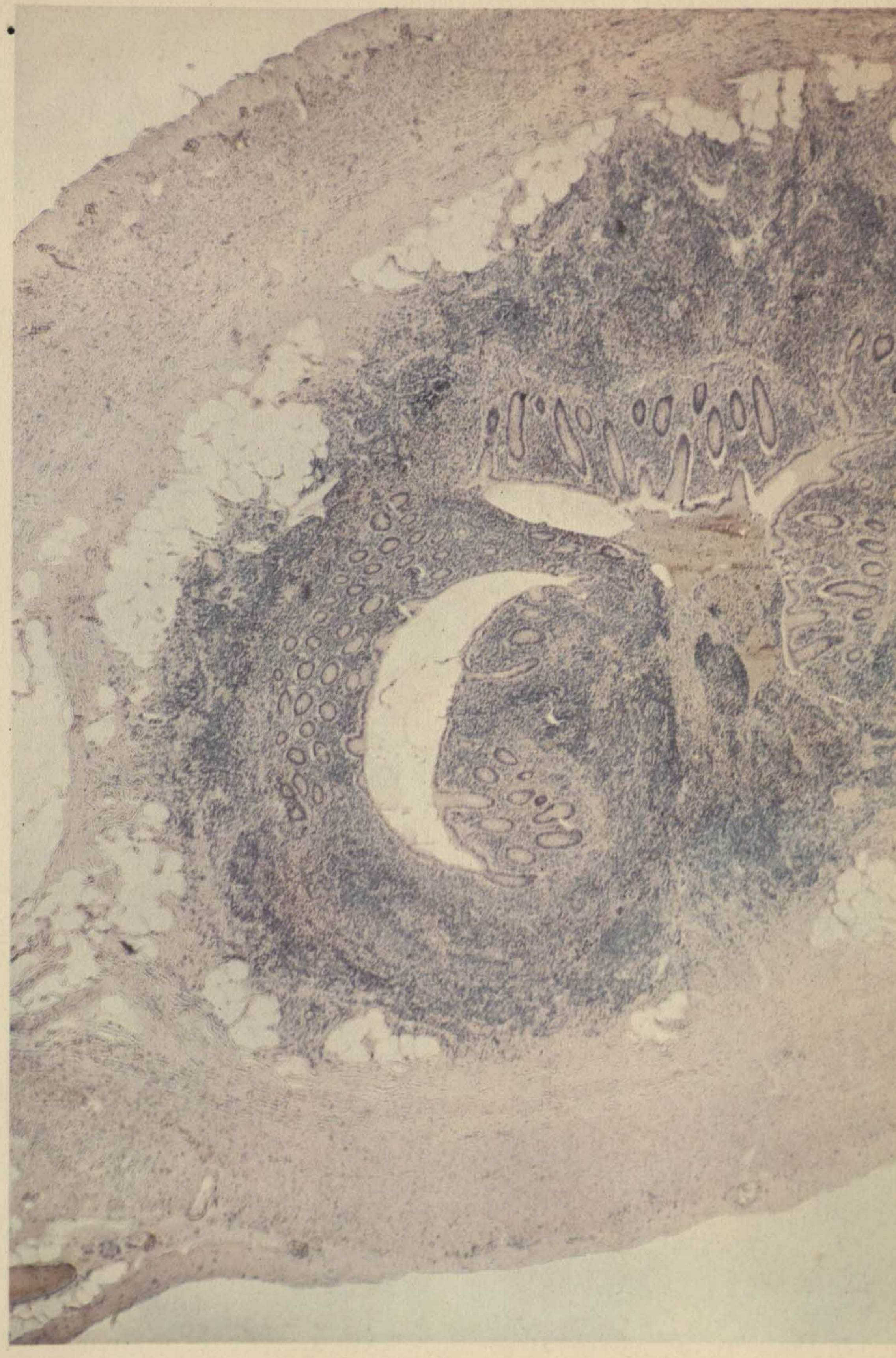

*Fig. 4. Appendectomy is without doubt the commonest and least dangerous excision. Above, a photograph of the tissue of the appendix at the time of crisis: the section has been taken through a focus of suppuration. (Photo Lod, taken at the Hôpital St-Antoine, Paris).*

Anatomical studies have also made possible the excision of segments of an organ such as the liver, of which the complete excision is inconceivable. Partial hepatectomies have been practicable only since it has become possible to define the limits of the segments with autonomous blood supply, which can be removed without damaging the remaining parenchyma.

The aim of modern surgery is to reduce to a minimum the mutilation caused by excision, and this applies not only to physical mutilation. The surgeon's solicitude should go further. He must consider also the psychological consequences which the idea of mutilation can have on the patient, even when mutilation is benign and leaves no physiological ill effects. Few patients are intelligent enough or sufficiently well balanced psychologically to be able to take an objective view of the medical problems and to withstand the psychological repercussions of even an ordinary operation. Any persons suffering from neurosis or anxiety who cannot understand the nature and consequences of an operation are likely to find their psychological troubles aggravated after surgery. The psychosomatic effects of operations are far from negligible. Every surgeon is familiar with the type of patient whose emotional reaction has compromised the effects of even a successful operation and who believes himself to be irremediably affected.

In contrast with the excision of benign lesions, which are necessarily moderate and limited, ablations of malignant tumours tend to become more and more extensive. Yet today, in the treatment of certain cancerous lesions, extensive excision is the only means of success. But in the public mind absurd convictions often exist about such operations—convictions which are propagated by the ignorant or by persons interested in the persistence of such errors. According to the type and situation of a malignant tumour, surgery can achieve 10 per cent to 80 per cent of definitive cures. In certain forms of extreme malignancy, which at one time always appeared to be fatal, exceptional successes, or at least prolonged remissions can be achieved. In the present state of total ignorance about the nature and origin of cancer, surgery, whether or not associated with radiation treatment, remains the only effective weapon.[4]

The problem set by ablative surgery of certain very advanced cancers is whether to risk killing the patient at once in order to avoid a slower and inevitable death. In certain cases, which ten years ago would have been considered inoperable, this is a very grave decision to have to make, even today, when extremely formidable operations are justified by the number of lasting cures. With ten such cases in mind, for example, has the surgeon the right to expose two to immediate death after the operation and leave seven without any improvement, in order to save one? In the past, all ten would have been left to die of their disease.

## *The future of ablative surgery*

Ablative surgery is a last resort; the removal of an organ is only undertaken when it has been established that a lesion can be cured by no medical means. But it is possible that the field of ablative surgery may be reduced in proportion to our progress in pharmacology and physiology. In other directions, paradoxically, it may become extended. Gastric ulcer and tuberculosis of the bones, in this connection presents two diametrically opposed examples.

It used to be the practice to treat an ulcer of the stomach in a conservative manner by diversions such as anastomoses of the digestive tract. Then, when surgery became safer, removal of the stomach was more favoured. Today, however, there is a return to favour of medical treatment and of old types of operations performed in the light of a better knowledge of the physiology of patients suffering from ulcers.

In tuberculosis of the bone, a direct attack on certain foci used to be considered impossible, as, for example, on foci in the vertebrae in Pott's disease. But since pharmacology has provided us with antibiotics that are effective against the tubercle bacillus, ablative operations can complete the medical treatment by ridding the bone of the remaining tuberculosis foci that have become bacteriologically inactive.

Ablative operations will remain essential tools in surgical therapy. Their importance will chiefly be in relation to traumatic, infective, or benign neoplastic lesions. So far as malignant tumours are concerned, the logical basis of surgery is disputable. Only the discovery of the inherent nature of cancerous processes will see the disappearance of ablation—to the profit of biological or chemotherapeutical treatment. Will ablative surgery retain, perhaps, a complementary role in the treatment of malignant tumours, as it has done in the treatment of tuberculosis?

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*to remove both the gall-bladder and its calculi. With pancreatic lithiasis the problem is quite different. Removal of the pancreas is a very serious operation, not to be undertaken without having given full consideration to the possibility of a less drastic palliative operation. Again, how can one decide about a fibroma of the uterus, which is a benign tumour? Clearly, the simplest thing is to remove the whole uterus with the fibroma, an operation that is relatively harmless, well-known and routine. But it is also a mutilation of the patient. Would not a more limited and more logical operation do instead—the removal of the fibroma only, so as to preserve the uterus? In many cases this would certainly be the answer, especially if there is only a single voluminous fibroma that can be easily removed. But this limited form of removal, known as myomectotomy, involves risks of haemorrhage or infection from which hysterectomy is free. Although it has advantages for a young woman, it has few for a woman at the menopause. The choice here will therefore depend on the type of fibroma, its precise position in relation to the uterus, and on the age and possibly even the wishes of the patient.*

(4) *It might appear that if the diagnosis has been made at an early stage and if the lesion is still very limited, a restricted and relatively harmless operation will suffice. Unfortunately, this is far from being the case, because there is still no means of determining the exact limits of the metastases in the lymphatic glands, and it has been said that the most circumscribed cancers require the most radical excision; extensive or very extensive tumours may require excision on such a large scale that in spite of improved means of resuscitation and anaesthesia, considerable risk is involved and the chances of a cure are definitely reduced. If the chances were not reduced, the problem of what treatment is indicated would be easily solved. Unfortunately this is not so.*

# Traumatology ·

Robert MERLE D'AUBIGNÉ

*The progress of science has reduced the extent, and in some cases even resulted in the disappearance, of some branches of pathology, and others will inevitably dwindle. But whatever safety precautions are developed and adopted there is little hope that we shall see a diminution in the number of accidents. Although better organization of working conditions in industry and the improvement of machines must reduce the frequency and gravity of industrial accidents, these improvements are bound to be offset by increasing mechanization and the spread of engineering techniques in trade and agriculture. At the same time, the multiplicity of means and greatly accelerated speeds of transport, together with indulgence in violent or high-speed sports, contribute more and more to the rising accident rate.*

Some figures may give an idea of the importance of the problem. There are in Great Britain nearly 400,000 road casualties a year, including more than 7,500 deaths; and approximately 9,000 fatalities occur annually in the home. Industrial accidents (an industrial accident is officially recognized as one that causes more than three days' disablement) result in at least half a million people being injured every year.

The cost[1] of the treatment and, indirectly, of compensation for the great majority of these accidents falls on the taxpayer. The cost is all the heavier because most accidents happen to young people, and permanent disablement represents not only the cost of compensation or of providing a pension, but also the loss, which is incalculable, of productive work.

## *Treatment of casualties*

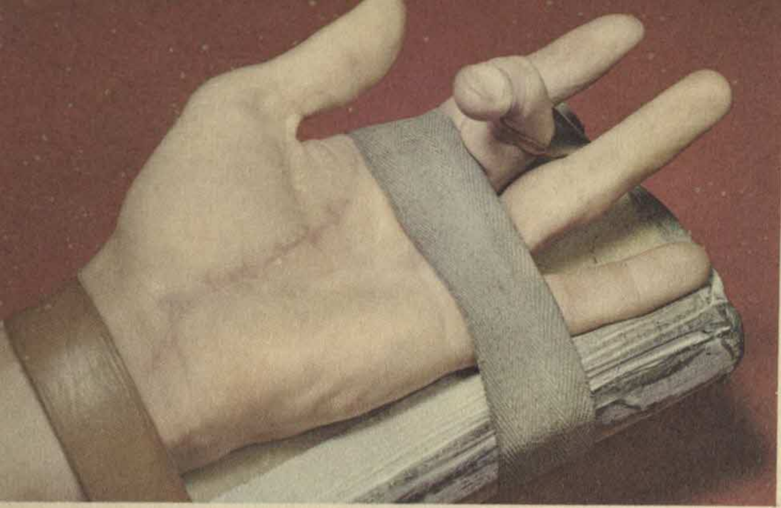
To estimate how far, in a modern society, existing hospital services have become incapable of efficient provision for people injured in accidents, it is necessary to assess the changes that have occurred in the nature of accidents and in the methods of treating them.

Apart from the various types of accident that have long been familiar, others of an altogether different kind now occur as a result of the great increase in and faster speeds of methods of transport. When a vehicle travelling at high speed collides with a fixed object, the violent deceleration is likely to result in multiple lesions of considerable gravity. Often, there are combined lesions of the skull and chest which immediately endanger life, and multiple lesions of the limbs, each of which may cause grave disability if it is not correctly treated.

At no matter what hour of the day or night they occur, these serious multiple injuries need immediate treatment and modern therapeutic methods to cope simultaneously

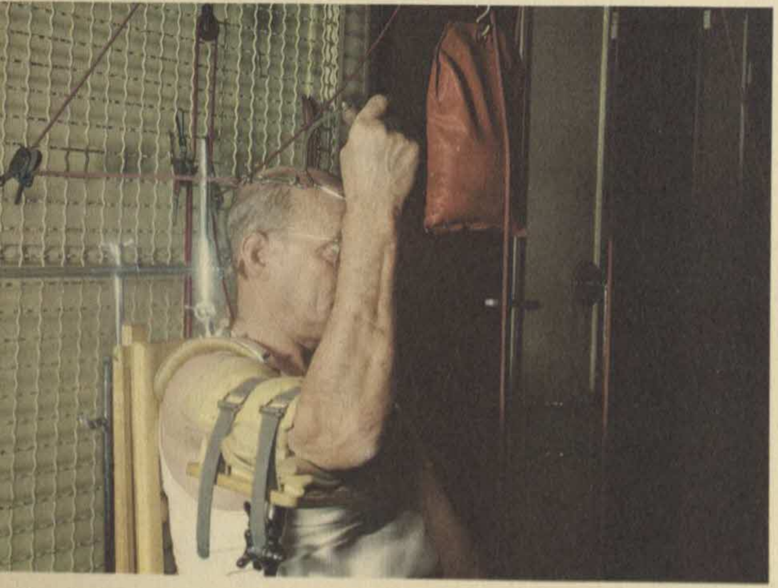
(1) *In France, the cost to the community of caring for people injured in accidents, and of compensation for traumatic disabilities, is estimated at an average of about 300,000 million francs a year, or £22,500 million. According to the experience of other countries, it seems not unlikely that this expense could be reduced by almost a half by a rational organization for the care of victims.*

# Functional

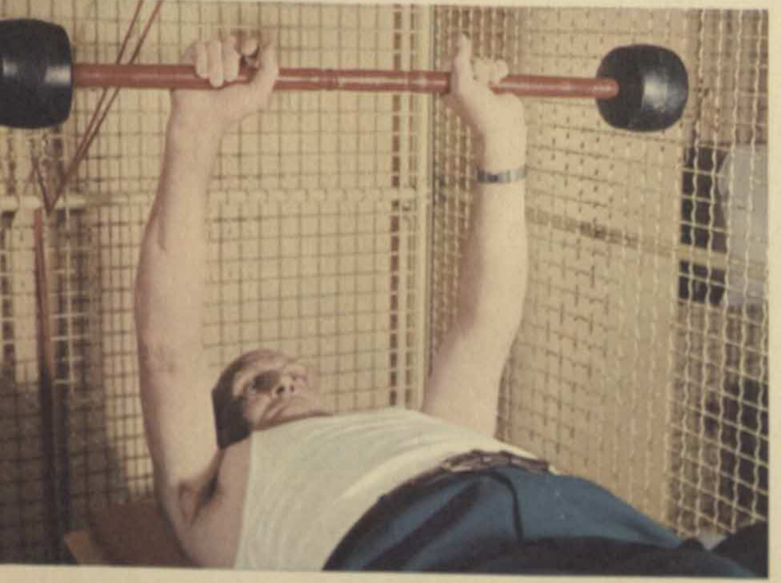


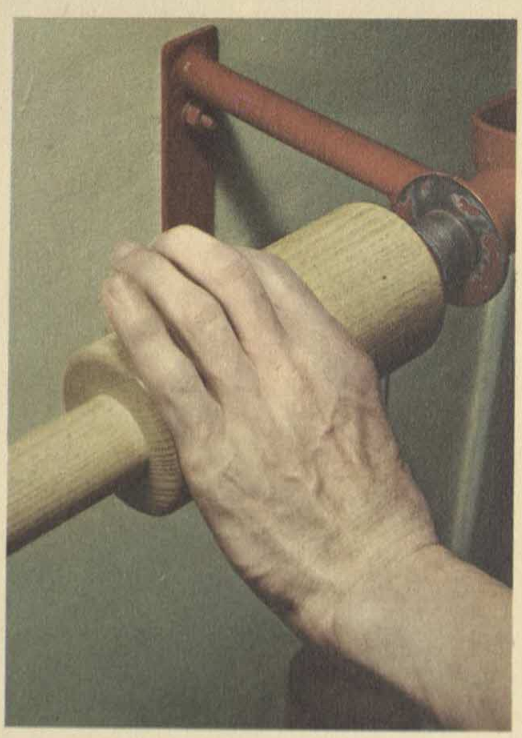
*Re-education of the flexors of the middle finger. The hand is immobilized on a small board by straps. Resistance is provided by a rubber band attached to the middle of the finger.*

*Re-education by pulley-treatment of the triceps muscle, the extensor of the arm.*



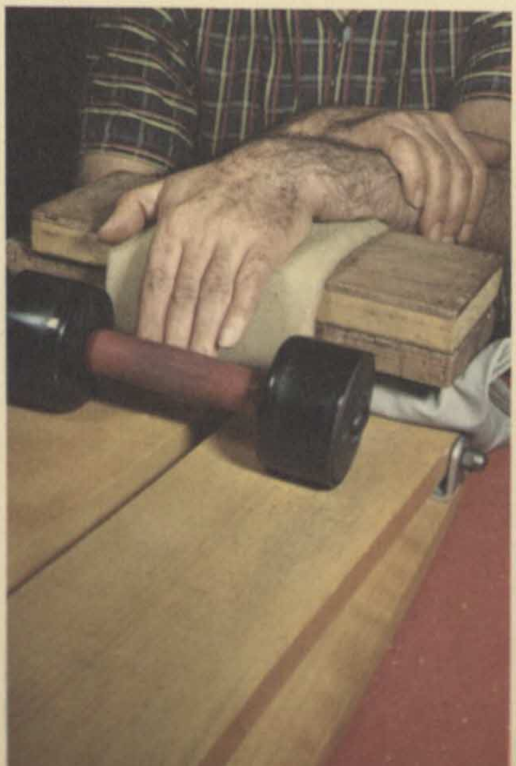
*Re-education of the shoulder: simultaneous active-passive elevation of the two arms.*

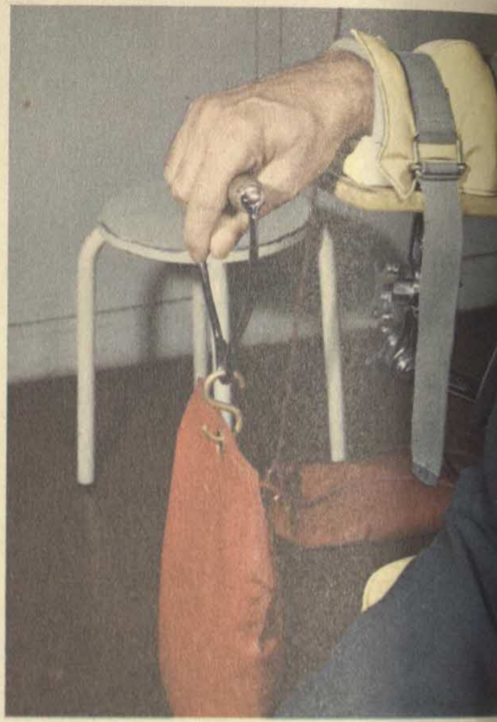




*Re-education of flexion and extension of the wrist by the windlass system (also called the Andrieu bobbin system).*

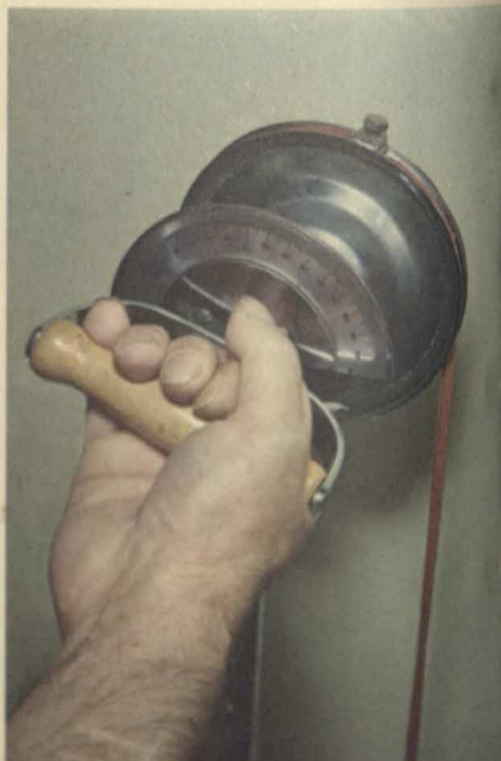
*Here, in order to re-educate the extensors of the fingers, the patient is pushing up a dumb-bell placed on an inclined plane.*



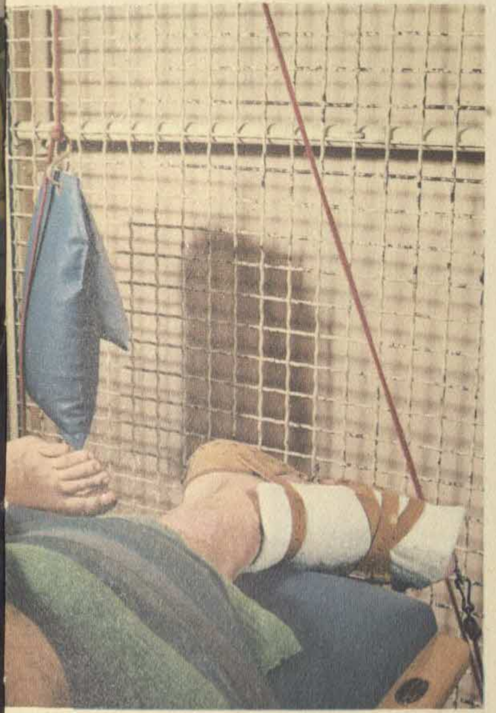


*Re-education of extension of the wrist; the forearm is firmly fixed to a board by straps.*

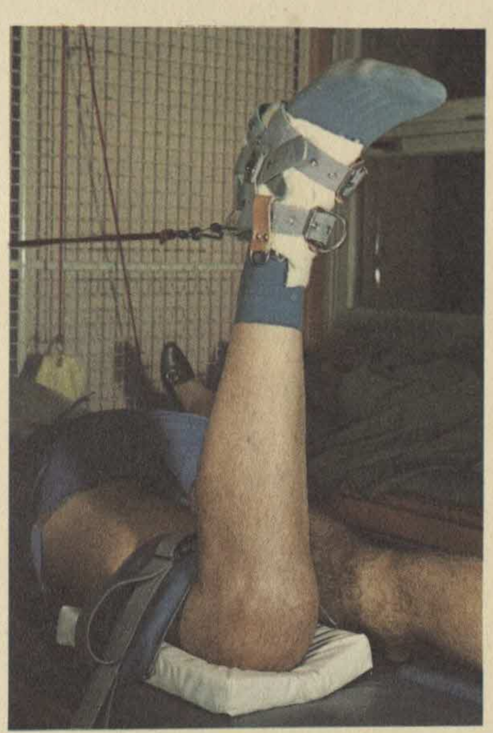
*With the hand gripping the handle of the apparatus, the patient alternately turns the palm upwards and downwards. He thus re-educates the pronator and supinator muscles.*



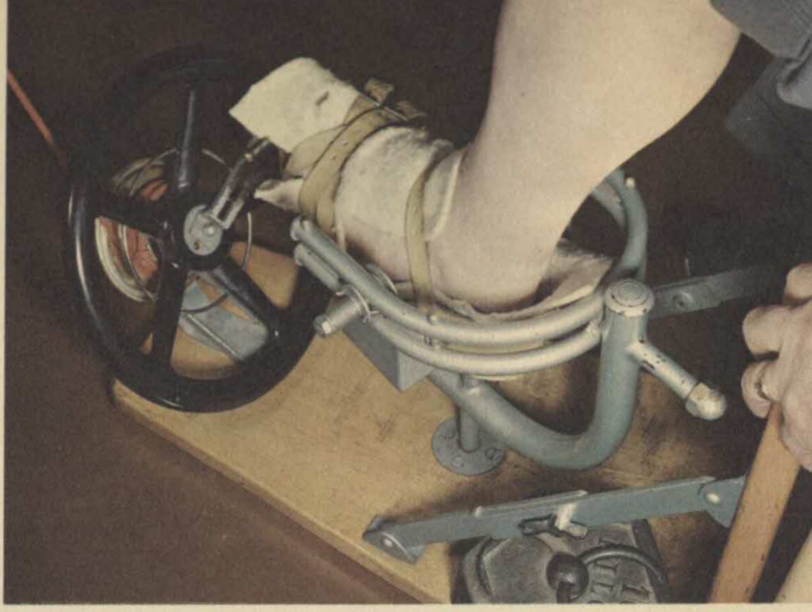
# re-education



*Active re-education of the adductor muscles of the foot, especially of the tibialis anterior, by a system of pulleys.*



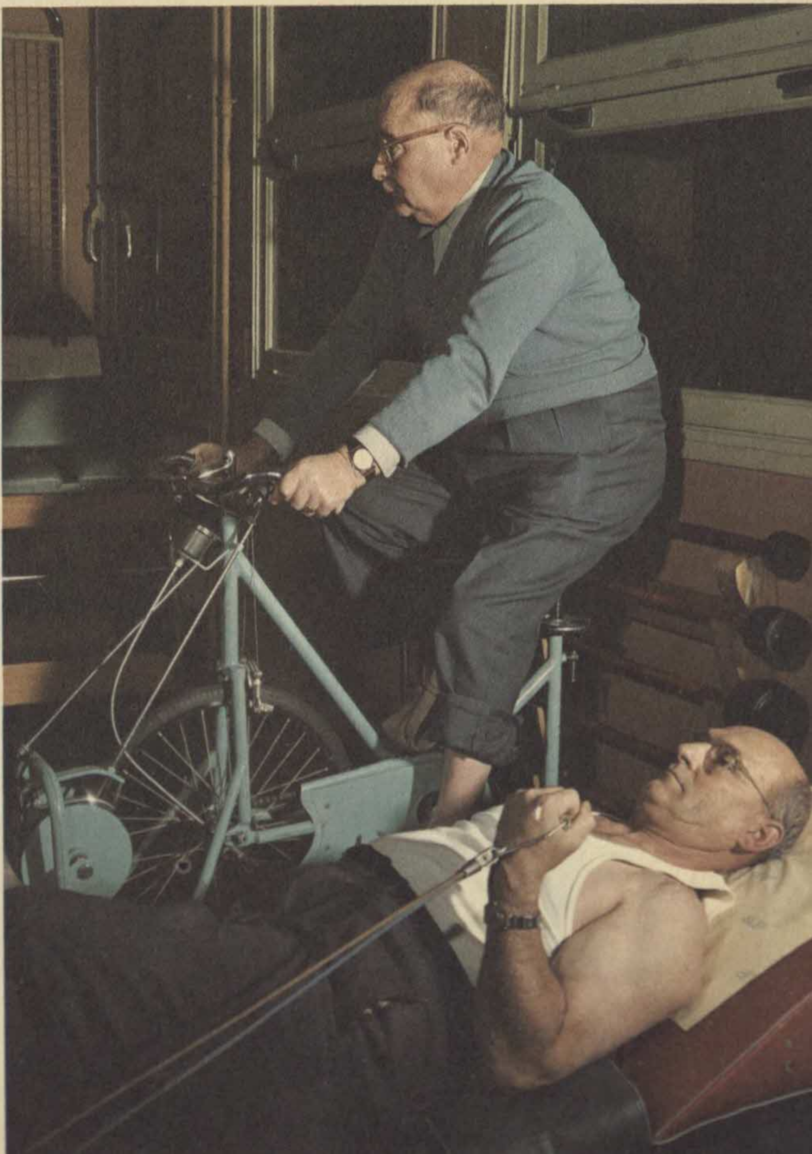
*Active re-education of the quadriceps, the group of extensor muscles of the leg on the thigh. The patient, lying on his stomach, is working in the extended position.*

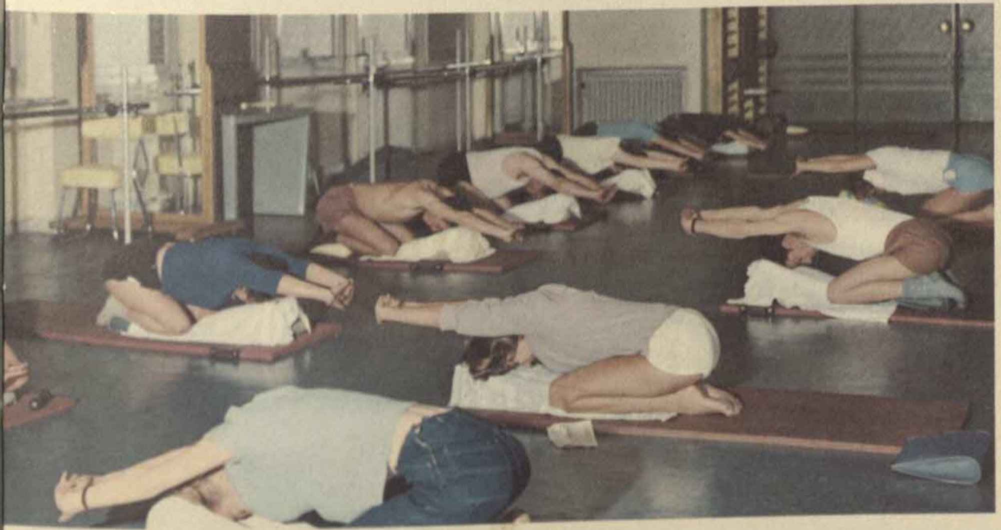


*The ankle is re-educated by mechanical rotatory movements.*

*All treatment for traumatism must logically be followed by early and active re-education, so as to re-integrate the patient as quickly as possible into the cycle of his social and professional activities. (Photos by Lod, taken at the Service de Rééducation du Centre de Traumatologie, Pavillon Ollier, Hôpital Cochin, Paris).*

*In active exercise of the flexors of the arm (biceps, brachialis muscles) the resistance is provided by an elastic cord (Sandow). Behind, active movement of the hip and knee on a bicycle.*





*Group exercise: gymnastics which reverse the curvatures are recommended to reduce kyphoses and lessen lumbar pains.*

with cranial and thoracic or abdominal lesions and limb injuries.

Methods of treating injuries have made considerable progress. These methods have two aims: to preserve life, and to avoid disability, which can be achieved by the satisfactory knitting of fractures, the preservation of mobility in the joints, and the preservation or re-establishment of the functions of nerves and muscles.

The vital problem of saving life presents itself immediately after the injury, and sometimes during the following few hours or days. The method of coping with this problem is essentially what is called resuscitation.[2] This consists, first, in giving immediate transfusions to compensate for the loss of blood and in re-establishing respiration[3] and circulation. Other essential procedures, which are often more complex, are the maintenance of urinary excretion and of the general equilibrium of the tissues and the blood: these problems are present in most serious injuries and also in cases of extensive burns.[4]

There are other problems hardly less urgent in the case of the seriously injured person whose life is endangered: these include the reduction of dislocated large joints and fractures, the cleaning and disinfection of wounds, and the preparation of adequate equipment for the treatment of lesions of the limbs or vertebral column. For all this, an expert medical team and trained helpers are necessary, together with extremely complex equipment for bone surgery or the orthopaedic treatment of fractures.

The classical methods of immobilization by traction or in plaster, which are always in use, with improvements, are nowadays reinforced by operative surgery which, efficacious though it may be, is nevertheless risky. Osteosynthesis[5] has the immense advantage of permitting controlled reconstitution of the bone and maintenance of the mobility of the joints; but it can be disastrous if it is complicated by infection; if union is delayed, recovery may take a very long time.

A comparatively recent and most interesting method of treating large fractures of the limbs is by the insertion of strong metal pins in the hollow cavity of the bone, which completely immobilizes the region of the fracture but not the joint. This device, which avoids the patient having to spend a long time in bed, enables him to avoid stiffness of the joint and also to make a rapid return to his normal activities. But as each pin must fit exactly into the fractured bone, this method makes it necessary to have a number of pins in stock and ready for use.

## *Bone grafts and the bone bank*

In certain cases, if part of a bone is destroyed by an accident or deprived of its blood supply, it must be replaced by a 'prosthesis', or piece of metal. Nowadays, prostheses are usually well tolerated, but their shape must be meticulously prepared in each case (they all have to be made of a special metal) and as they cannot be made quickly to order, it is necessary to keep a considerable stock of them in hand.[6] Sometimes the bone-substance itself has to be repaired, but the patient cannot always provide a bone 'graft', and it is then necessary to use a 'bone bank'.[7]

There are, of course, other lesions that affect the tissues, such as those of the blood vessels, nerves, muscles or tendons. For the repair of lesions of the peripheral nerves and of the tendons of the hand, in particular, extremely delicate techniques are necessary. These can be acquired only by very considerable practice and to get the best results they must be performed by a specialist.

The problem of functional re-education plays an essential part in the recovery of accident victims. Besides surgical and orthopaedic methods to ensure the knitting of a bone or the healing of wounds or contusions, it is necessary to maintain the working of the tissues, especially the muscles and nerves, by ensuring that these are kept functional and adequately exercised under supervision. This re-education must be started early and continued until the injury is healed.

One of the essential principles of re-education is to influence the patient's psychological state by getting him to participate actively in his own cure; it is also necessary to shield him from the feeling of indignant demand for compensation, which is very common among people who have been injured and more or less left alone, and which invariably results in a worsening of the less severely injured patient's condition. Re-education requires a complex organization with enough staff to treat each particular case until the cure is sufficiently advanced for the patient to join in group exercises.

The importance of this type of organization is that it ensures the right kind of care, both as regards the urgency and the continuity of treatment, with therapeutic equipment always available at once. But such provisions can be made only in important centres, to

(2) *On this subject, see the chapter by Professor Jean-Pierre Soulier on page 50.*

(3) *Machines have now been perfected which make it possible to maintain respiration, and therefore life, for several days or weeks, pending the re-establishment of the normal vital reflexes.*

(4) *All up-to-date systems of resuscitation require a specialized staff of doctors and medical assistants, especially nurses, trained in modern methods of treatment. Buildings should be specially equipped; each bed must be isolated and provided with everything needed to ensure artificial respiration, oxygenation, continuous transfusions, and the aspiration of particles and mucus from the respiratory and digestive cavities.*

(5) *Osteosynthesis: fixation of the bone by mechanical means after reduction of a fracture.*

(6) *In order to keep the considerable amount of equipment, and the trained staff who are to use it, available for the treatment of accidents at all hours of the day and night, the considerable cost involved (not only in running expenses but also in the immobilization of capital) must obviously be offset by a sufficiently large number of casualties.*

which the more serious cases of injury can be sent and where they should be looked after in wards.

At present, even in highly civilized countries, this form of organization scarcely exists. One of the most advanced countries, Austria, has, however, built nearly twenty specialized accident centres since the end of the last war. Italy also has recently opened a large number of centres for orthopaedics and accident cases. In France, however, there are fewer than a dozen such centres, and in England, according to a report issued in 1960 by the British Orthopaedic Association, 'the organization for the treatment of people injured in accidents remains seriously deficient'.

## *The casualty centre*

Throughout every hour of the day and night there must be available not only a surgical unit complete with anaesthetic equipment, resuscitation facilities, and a laboratory, but also X-ray apparatus, complete surgical equipment, and a staff trained in the use of these various appliances and in the preparation of plaster, etc.

## *Specialization*

Because of the frequency and gravity of accidents and the progress in medical and surgical techniques, advanced specialization is often urgently necessary. In most cases, the types of surgery involved are neurosurgery, thoracic, abdominal and orthopaedic, but sometimes stomatology, otorhinolaryngology, ophthalmology, and urology are also needed. Ideally, a casualty centre should therefore be established in a general hospital where these various forms of specialized treatment will be available; but the uses made of them will be very unequal. In an average intake of casualties, including those injured in industrial and road accidents, it is likely that in about 150 out of 1,000 cases the neurosurgeon's advice will be needed, but his intervention not more than once or twice. The thoracic surgeon will be called upon perhaps twenty times, but will operate only twice; and ten cases will need abdominal operations. Out of this total of 1,000 cases, probably not more than fifty will be free from injury to the vertebral column, the pelvis, or the limbs. The functional result will depend on the rapid recognition of these lesions and on their subsequent and prolonged treatment. The appropriate forms of orthopaedic treatment—extension, plaster, osteo-

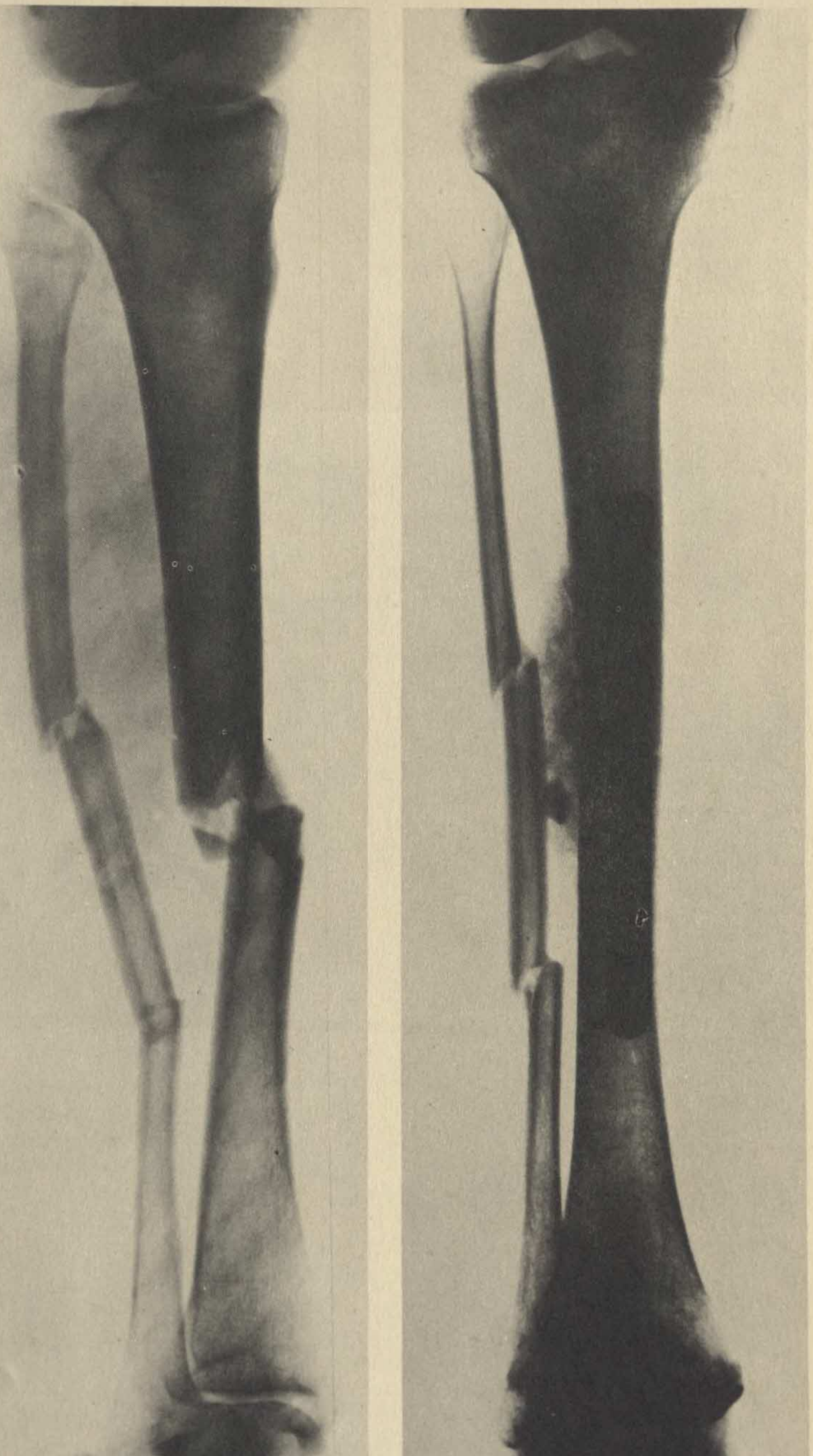


*Fig. 1. Comminuted fracture of the leg: the tibia (four fragments), the fibula (a double fracture with an intermediate piece). In order to obtain a perfectly straight leg and consolidation under good conditions, a surgical operation is necessary. Osteosynthesis has been carried out with a screw-plate, the four screws of which are seen in the right-hand photograph. The second photograph, taken several weeks after the operation, shows the callus in process of formation.*

synthesis, and motor re-education—will thus need to be applied to 95 per cent of the injured.

This is why the casualty centre in a general hospital should be attached to a department of surgery of the locomotor system. It will direct to the appropriate departments the rare cases which do not come within its province and will call for the aid of different specialists in the frequent complex cases, and it will remain in charge of the case until the injury is cured. This, of course, necessitates an out-patient service—an organization to carry out re-education.

## Out-patient services

Patients whose upper limbs have been injured, as well as a large number of those with injuries of the lower limbs, can be treated as out-patients provided that they are regarded as urgent cases. An injured person should, ideally, be assigned to the same doctor throughout the whole of his treatment. This rule, derived from the principle of sole responsibility for a patient, is necessary if satisfactory results are to be obtained.

## Re-education of injured patients

If immobilization is indispensable for the consolidation of fractures, voluntary movement is indispensable for the conservation or recuperation of muscles, nerves, and the circulation—in other words, for the life of the injured limb. The principal treatment, by muscular contraction, must be started from the very beginning (without waiting for removal of the plaster) and should be carried out by a re-education staff directed and controlled by the doctors. A country centre for re-education after surgical supervision has ceased should be attached to the urban centre. Also there must also be close co-operation between the hospital authorities and organizations for re-classification of persons who have disabilities which debar them from doing their former jobs.

## The instruction of personnel

The importance of establishing centres for teaching how to deal with casualties is obvious. The grouping of numerous injured patients within a service organized for this purpose makes it possible to train a staff that is competent at all levels of re-education. Male and female nurses, as well as therapists, will quickly be able to acquire both knowledge and experience. Future doctors will learn how to treat simple cases of the sort for which they will often be responsible, especially in country practices, and how to distinguish such cases from the more complex ones in which they will need to call in a surgeon. The surgeon himself will be able to see, grouped together, a large number of cases, involving difficult and exceptional injuries, within a relatively limited time.

## The need for a casualty organization

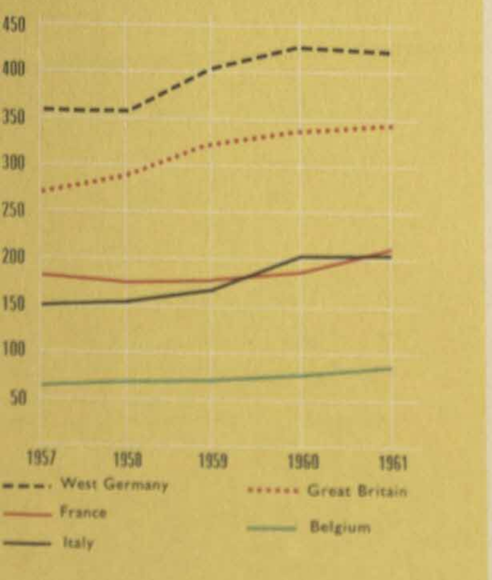
As soon as such centres are established, a problem that arises is that the number of injured who need treatment is so large, and the attraction towards these centres is so great, that they are often overwhelmed with minor accident cases which they cannot refuse but which hinder them in treating the more serious cases for which their services are vitally important.

The creation of specialized centres—which is necessarily the first step within an organization—will only be effective if the centres, of which there are two types, form part of a general organization for dealing with accidents:

(a) In built-up *urban* areas distance does not matter; the organization should be planned only on the size of the population. A population of a million will need, at most, two such centres for accidents and emergencies. Ideally, the centre should be in a general hospital. A large resuscitation centre for the treatment of shock and for giving respiratory resuscitation, manned by a permanent staff working in shifts, provided with departments of internal and orthopaedic surgery, will ensure that surgeons are in charge from the start of a case until the patient is well enough to be discharged.

In a community of 500,000 to 600,000 inhabitants provided with large well-organized out-patient departments, 150 beds should be adequate for the treatment of serious accidents requiring limb surgery. The same number of beds should suffice for the reception of all cases requiring surgical treatment in a community of 180,000 to 200,000 inhabitants. In towns, the concentration of all emergency services for dealing with accidents or other cases in well-equipped centres, and the treatment of all limb and spinal injuries in special orthopaedic departments would seem to provide the best solution.

(b) In *rural* areas, where the population is dispersed, such a concentration of facilities would be impracticable for two reasons: a seriously injured person may not be able to



*Graph showing the number, in thousands, of people injured by road accidents in various European countries.*

(7) *Pieces of bone taken from a dead body soon after death are kept at a low temperature in a refrigerator.*

survive a long journey or a delay in treatment; also, it is often impracticable for patients with minor injuries to travel far from their homes. It would seem therefore that three graded categories of organization are necessary:

1. *Emergency centres* for *first aid*, which should be numerous enough for a seriously injured person to be taken to one in not more than half an hour: this agrees with the distribution of non-specialized surgical centres.

A sufficient number of non-specialized surgical centres should have resuscitation equipment and be ready for the treatment of abdominal emergencies, whether caused by accidents or otherwise. After first aid, serious cases, especially those involving a risk of permanent incapacitation, would be sent on to one of the specialized centres.

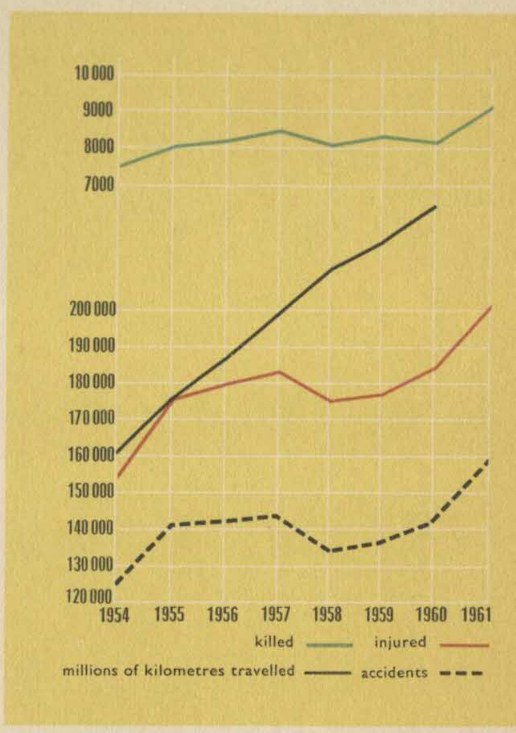
2. *Specialized centres* in second-line support should deal with all cases needing surgery for serious traumatic lesions of the limbs and vertebral column, together with non-traumatic lesions of the locomotor apparatus. Such a grouping, apart from being of great benefit both to ordinary patients and accident victims, would enable many hospitals, probably one in three, or even one in two, to specialize in locomotor surgery.

3. *Regional centres* in third-line support. These would necessarily be located in large towns and would provide the local population with the facilities offered by the other two categories, and also receive from the latter the most serious cases in their regions. These cases (spinal or complex fractures of joints, with nervous complications, or nerve lesions), could be speedily transferred, or at least as soon as possible; cases with complications or in which treatment had failed could be transferred later on.

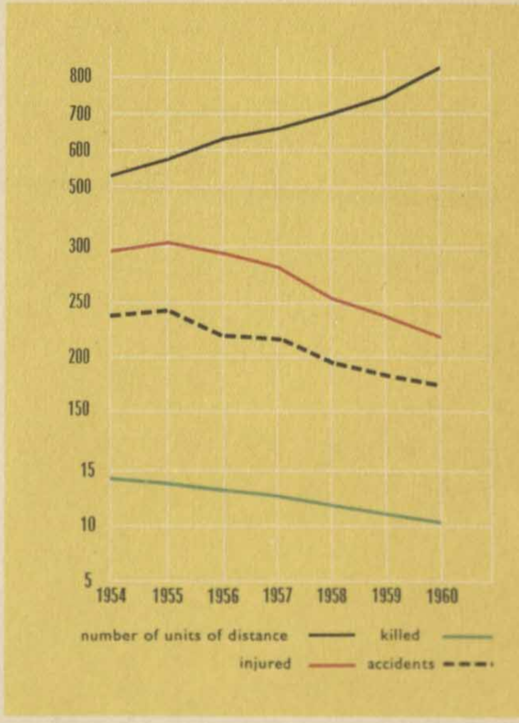
Two types of problem are likely to arise, the one medical, concerning staff, the other administrative and financial.

With regard to the first, doctors are naturally independent and often sensitive, and difficulties that may arise because of this will not be overcome by regulations or restrictions. They can be best resolved in connection with the level of teaching and scientific work. It should be easy to establish understanding and collaboration between doctors and surgeons who have studied or undergone their specialist training together and who would frequently meet to pool their experience and draw lessons from them. This spirit of collaboration would be encouraged by the attachment of specialized centres to emergency centres at regional level, which would relieve casualty staffs of their most serious problems. This arrangement would be of special benefit in cases of extensive burns, paraplegics, chronic osteo-articular infection, and fractures in old people. Experience has proved that there is never any difficulty in transferring cases such as these from one type of centre to another.

Financial problems should present fewer difficulties. Although the organizational and installation costs of a well-equipped casualty centre may be very high, the saving that would result from a reduction in the amount of time spent on treatment and the time spent away from work, as well as money spent in sickness allowances, would no doubt more than cover the expenses involved. Experience has shown this to be so in countries, notably Austria, where a comparison has been made between the cost of treating patients in specialized centres and treating them in general hospitals. The economies resulting from treatment in specialized centres have encouraged the authorities to set up more and more of them. It seems, therefore, that development along these lines ought to be practicable everywhere, and that in view of the increasing importance of the problem, owing to the multiplicity of accidents, this will be its ultimate solution, both from the humane and the economic point of view.



*Graph showing the number of accidents, and people killed or injured in France.*

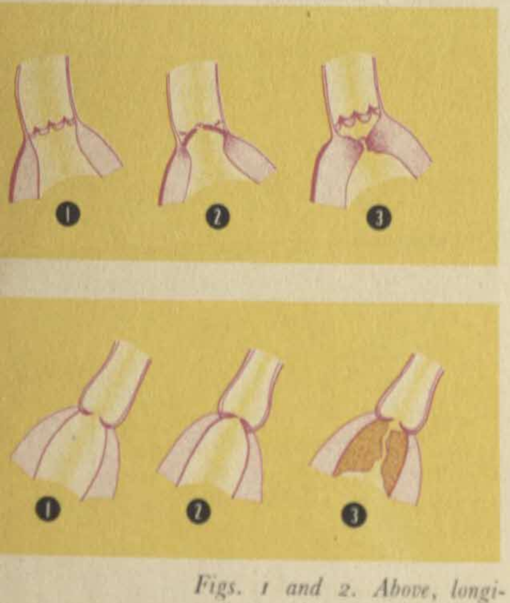


*Trends in the rates of accidents and of killed and injured per 100 millions of motor-car-kilometres travelled in France.*

# Congenital heart defects

### *Charles DUBOST*

*Not so very long ago, heart defects were largely disregarded in cardiology; for lack of any therapeutic treatment, they were regarded simply as anatomical and nosological curiosities. Although their embryonic development had been studied, and a distinction had been made between conditions involving the mixing of venous with arterial blood and those characterized by valvular stenosis of the channels, close anatomical description was useless as a guide to surgery because twenty-five years ago thoracic surgery was still in its infancy.*



*Figs. 1 and 2. Above, longitudinal section of the sigmoid aortic valves:*
*1. Normal valves; 2, stenosis of the valves; 3, infundibular stricture on the near side of the valves. Below, longitudinal section of the opening of the pulmonary artery: 1, normal opening; 2, stricture of the valves; 3, infundibulo-pulmonary stricture, leaving the valves intact.*

Children who had these defects were left to themselves; they were considered to be cardiac cases only at the final stage of their illness, when the weakness of the heart caused the well-known sequence of symptoms to appear; symptoms which responded only during a limited time to the customary medical treatment.

It was in 1939 that a Boston surgeon, R. E. Gross, made it known that for the first time he had successfully achieved the ligature of a persistent ductus arteriosus; doubtless he did not realize the full significance of this operation.

In 1944, H. Taussig and A. Blalock made a decisive advance by showing that an operation could be performed which would restore to children afflicted by 'blue disease' the possibility of reaching adult life.

In the same period, Crafoord announced that for the first time he had accomplished resection of a congenital stenosis of the isthmus of the aorta.

This was the period in which cardiac surgery was born; it was chiefly aimed at correcting congenital heart defects and resulted in an extraordinary renewal of interest in these conditions, which surgery can now at least ameliorate when it cannot cure.

Parallel with this development, a more detailed understanding of a wide range of lesions was provided by new methods of investigation, the most important of which was Cournand's method of catheter examination of the heart.[1] In 1940, Cournand had announced the results of his early researches, which gave others engaged in research, as well as those practising clinical medicine, an accurate basis for diagnosis.

Very soon, indispensable haemodynamic data[2] were added to the essential basic anatomical ideas; these can show the existence of a shunt[3] or of stenosis, or of hypertension or valvular insufficiency.

Angiocardiography[4] followed, and a little later cine-angiocardiography,[4] an improvement by which an actual image—at first static and then moving—of the lesion was provided to help in understanding the location and interpretation of lesions.

Thus surgery of heart defects continued gradually to develop. Operations at first performed on the large blood vessels outside the heart, and also palliative operations, have since been replaced by direct operations on lesions inside the heart, thanks to the conception and development of two remarkable techniques: controlled hypothermia and the artificial heart-lung.[5]

In less than a quarter of a century, surgery has succeeded in saving the lives of a large number of children who would formerly have been condemned to die. Arrest of the heart, interruption of the circulation for an hour, an hour and a half, or even longer; the repair, with scrupulous precision, of malformations inside the heart which had previously been untouchable; and then the renewal of life for the little body kept in hibernation—these feats are now performed regularly by cardiac surgery teams.

The aim of this short chapter is to give an outline of each of the principal congenital heart defects and to indicate the surgical action that can be taken, it being impossible to separate the simple term 'congenital defect' from the idea of surgical correction.

## *Causes of heart defects*

Although congenital defects represent about 1 per cent of autopsies, this percentage increases down the age-scale until it becomes 8 per cent among children who die during the first month of life.

Among children, congenital defects which are the commonest of heart ailments account for 10 per cent to 50 per cent of all heart defects, according to their place of origin. Statistics indicate that, broadly speaking, about 1·5 per cent of new-born children have a congenital defect of the heart.

The causes of these defects are still obscure: embryology shows that the great majority of them are formed and become established during a brief period of foetal life, between the first and third months, and that they are due to disturbances or arrests of development. Both hereditary factors and extrinsic agencies (toxic, endocrinal, infective) are adduced to explain their development, but these possibilities are too vague and too obscure to enable us at present to lay down precise measures for their prevention.

## *Classification of malformations*

To the purely anatomical classification first used, a more recent physiopathological classification has been added; this is based on the results of modern investigations (catheterization, angiocardiography. It is possible to identify three chief groups of heart defects: those without a shunt; those with an arteriovenous shunt; and those with a venous-arterial shunt.

## *First group: malformations without a shunt*

These essentially affect the aorta and the pulmonary artery and their openings.

## *Anomalies of the aortic canal*

Anomalies usually occur as narrowings or stenoses, which may be situated at the level of the valves (valvular stenosis) or below them, in the infundibulum of the aorta[6].

The lesion, whether it be at the aortic opening or below it, obstructs ejection of blood by the left ventricle, which becomes hypertrophied. The resulting cardiac distress is proportional to the degree of the stenosis.

If, after clinical examination, this diagnosis is suspected, it may be confirmed by left-ventricular angiocardiography, which determines the exact site and degree of the stenosis.

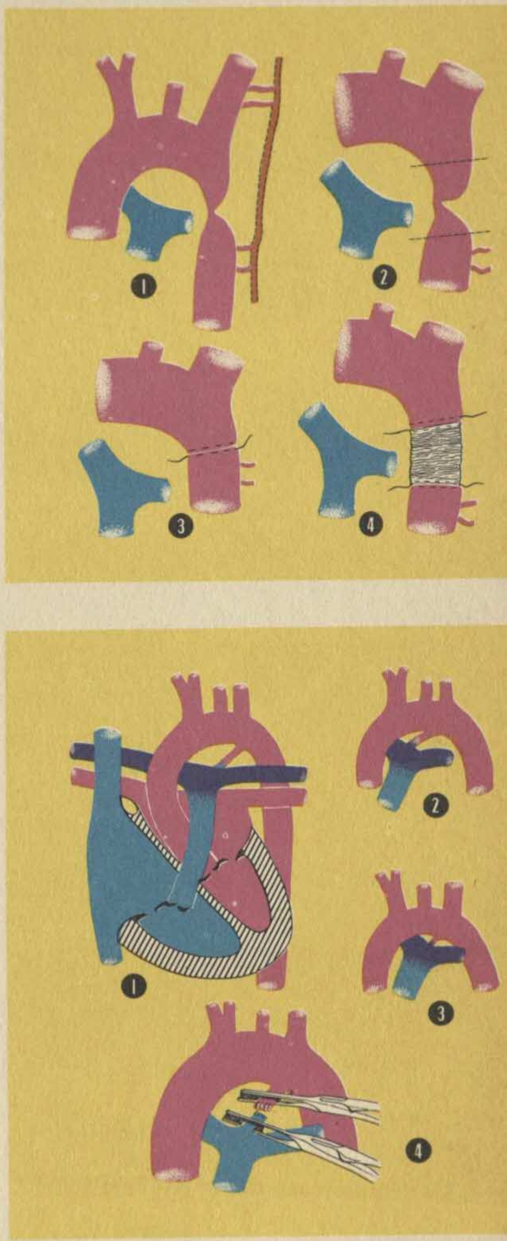
Treatment depends on the artificial heart-lung, to which deep hypothermia makes a vitally important contribution. When the patient's temperature has been lowered to 8° to 10°C, the circulation is completely cut off, the aorta opened, and the lesion identified. In a case of valvular stenosis, the valves are separated with scissors; if the stenosis is infundibular, the circular fibrous collar is cut out and removed so that a wide passage is provided for the blood.

If no operation is performed and the stenosis is causing considerable constriction, the child is unlikely to reach adult age.

## *Anomalies of the aorta*

Anomalies in the development of the aortic arches are rare malformations, but a congenital lesion which often affects the isthmus of the aorta is coarctation or stenosis of the aortic isthmus. This curious malformation interrupts the course of the blood in the aorta at the junction of its horizontal and descending segments. It causes arterial hypertension in the region of the head and the upper limbs with hypotension in the lower limbs and trunk; a difference which is partially compensated for by the development of a collateral circulation which unites these two parts of the body.[7]

The diagnosis established by clinical



*Figs. 3 and 4. Malformations of the aorta. Above, (1): coarctation, or stenosis of the isthmus of the aorta; 2 and 3 illustrate the operation which is performed when the resected portion is no more than a few centimetres in length: the aorta is simply sutured end to end. In certain cases (4) direct suture is impossible and a graft is then inserted, usually of plastic (dacron, teflon, knitted or accordion-pleated). Below (1, 2, 3), varieties of persistent ductus arteriosus. 4 illustrates the operation which consists in first occluding the ductus arteriosus between two clamps, then dividing it and suturing its two ends.*

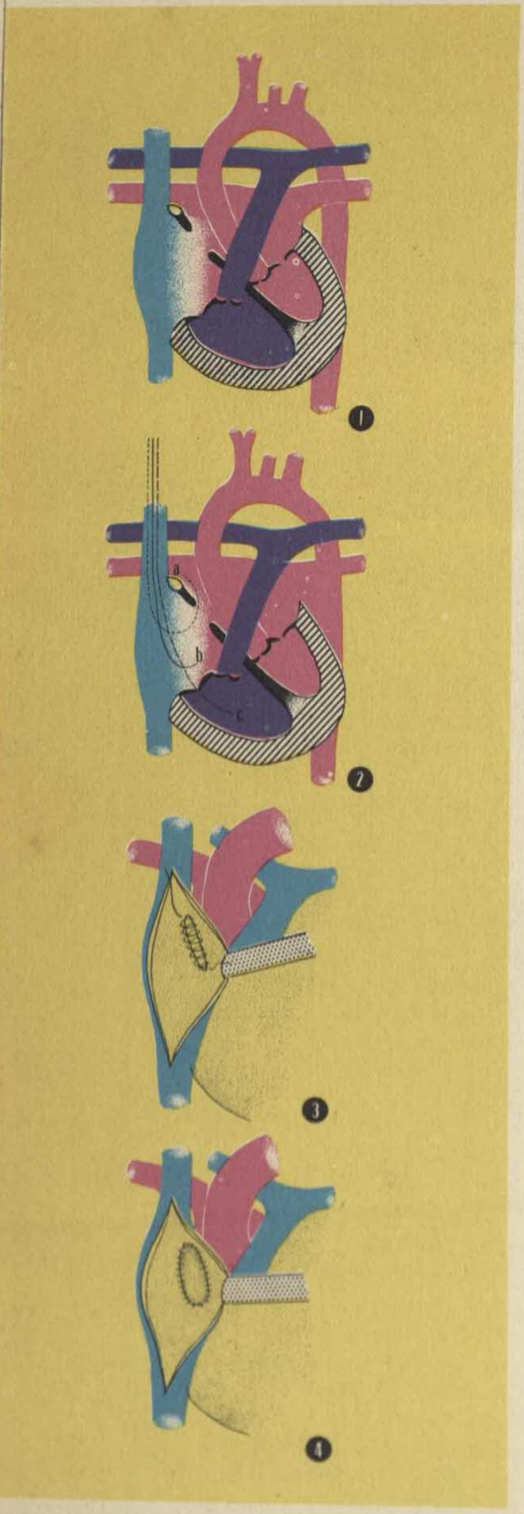


*Fig. 5. Interauricular communication ('Foramen ovale'); oxygenated blood of the left auricle mixes with venous blood of the right and returns to the lungs instead of into the aorta. 2 a catheter passed through the opening into the right auricle and right ventricle. 3, suture of the interauricular opening. 4, occlusion of the opening by a plastic plate stitched over it.*

examination (hypertension in the upper limbs, contrasting with absence of the femoral pulse and erosions of the ribs, indicating the existence of dilated and sinusoid intercostal arteries), may be confirmed by angiography, which determines the exact site and degree of the stenosis.

The treatment for this condition is surgical: it consists in resecting the stenosis to restore as wide a calibre as possible to the two segments of the aorta and to suture them to one another. In about 10 per cent of cases it is necessary to interpose a graft between the two ends of the aorta if they are too widely separated from each other.

The results of this operation are excellent and the mortality rate is very low. The restoration of a normal circulation protects the patient from cerebral complications or the heart failure that would threaten him if the operation were not done.

## *Anomalies of the pulmonary artery*

These consist almost entirely of anomalies of the pulmonary opening, usually called pulmonary stenoses.

The lesion may be situated in the aortic canal, at the level of the valves (valvular stenosis), or below them (subvalvular or infundibular stenosis). It forms an obstacle to the ejection of blood by the right ventricle, which hypertrophies and then becomes dilated.

The diagnosis, established by clinical examination, can be confirmed, as in the other cases, by catheterization and angiocardiography. When the stenosis is subvalvular, the treatment depends on the artificial heart-lung; deep hypothermia makes it possible to determine the lesions and to resect precisely the pad of tissue which partially prevents the emptying of the right ventricle.

If the stenosis is situated at the level of the valves, the cure is simpler: moderate hypothermia at 30° allows an arrest of the circulation for five to six minutes, which gives sufficient time to open the pulmonary artery and enlarge it by making two scissor cuts in the stenosed valves.

## *Second group: malformations involving an arterio-venous shunt*

These malformations are characterized by an abnormal communication between the two cavities of the heart or two vessels, which cause the oxygenated blood of the general circulation to pass into the venous blood of the pulmonary circulation. The result of this is what is called an arterio-venous shunt, directed from the left-hand or general circulation to the right-hand or pulmonary circulation; in other words, a left-right shunt.

## *Communications between two vessels*

The ductus arteriosus is a normal feature of the foetus *in utero* and is essential to its circulation; normally it is obliterated at birth. A failure to close may occur and will maintain a pathological circulatory condition by draining part of the blood in the aorta into the lungs. Persistence of this open vessel is easily diagnosed and may be proved by catheterization. Left to itself, this malformation may result in one of two complications; infection by *Streptococcus viridans*, or cardiac distress, which develops over a period of years.

The operation for relief of this condition was first performed by R. Gross in 1939; it consists of interrupting the continuity of the canal by ligature or by section and suture of the two ends. It is a benign operation, nowadays performed on thousands of patients to whom it restores a normal circulation. Most doctors agree in advising surgical operation as soon as the diagnosis of a persistent ductus arteriosus has been established.

## *Communications between the auricles*

Interauricular communications are the commonest of the congenital heart defects. The type which occurs most often is the persistence of the *foramen ovale*,[8] an opening which is always present in the embryo, but which is normally obliterated at birth. Besides this simple type, there are more complex forms, of which the most serious is the persistence of the *ostium primum* with or without a lesion of the mitral and tricuspid valves.

These communications are characterized by an increase, often considerable, in the supply of blood to the lungs, which is caused by the passage of blood from the left auricle, in which there is increased pressure, to the right auricle, in which the pressure is low.

In course of time, these abnormalities in the circulation cause distress of the right heart and damage to the arterial bed of the lung[9] and may end in severe pulmonary hypertension and a reversal of the shunt: but at this stage it is too late to operate. These lesions are easily diagnosed, the more so because catheterization provides anatomical proof of the shunt; that is to say, the catheter easily passes through the abnormal opening between the auricles.

In the simple forms, which represent the majority of cases, moderate hypothermia at 30° suffices: it allows an arrest of the circulation for five to six minutes, which time is used to open the right auricle and suture the edges of the abnormal opening; the risk in doing this is minimal.

In complicated cases with abnormal anastomosis of the pulmonary veins and damage to the mitral or tricuspid valves, the artificial heart is necessary in order that a longer and more delicate operation may be performed.

## *Communications between the ventricles*

Interventricular communications are less frequent than interauricular communications. Anatomically, they are almost always situated in the upper posterior part of the septum which separates the two ventricles (interventricular *septum*[10]), though very occasionally they are situated in the median part or base of this muscular wall.

Because the pressure in the left ventricle is higher than it is in the right, part of the blood in the former is sent into the cavity of the latter, from which it goes to the lungs: the bigger the interventricular communication, the more marked is the increase in the pulmonary blood supply, which causes damage to the pulmonary arterial bed and hypertrophy of the two ventricles.

Clinically, the diagnosis is established by a systolic murmur which radiates over the whole of the precardial area. Catheterization of the heart and left-angiocardiography may confirm the diagnosis and provide details of the haemodynamic conditions.

Operation is necessary if communication between the ventricle is of some magnitude. It involves the use of the artificial heart-lung, to which deep hypothermia makes a major contribution. The operation consists either of suturing the edges of the abnormal opening or of stitching a plate of plastic material to its periphery so as to close it up.

This is a delicate operation, but involves only a minimal risk, unless interauricular communication has caused a major pulmonary hypertension; the mortality rate in cases of hypertension is very high, hence the import-

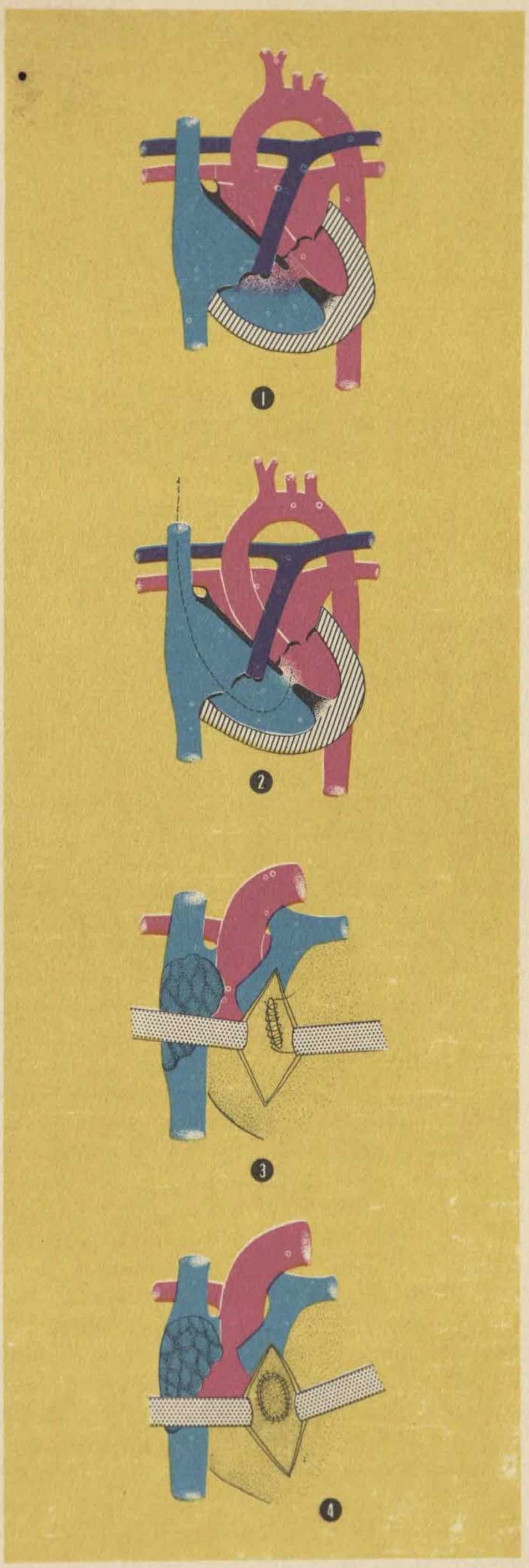


*Fig. 6. Interventricular communication: (1) the venous blood of the right ventricle passes into the left ventricle; mixed blood is therefore sent into the aorta. (2) the track of the catheter passing through the communication; (3) the closure by direct suture; (4) often a graft is necessary.*

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(1) Catheterization of the heart: *the catheter, a hollow or solid metal tube, was used until quite recently chiefly to investigate the bladder; its use has now been extended to the exploration of the cavities of the heart by means of a long slender plastic tube which is introduced along a vein of the arm in the direction of the heart.*

(2) Haemodynamic data *are those which are obtained by measuring the forces involved in the circulation of the blood.*

(3) Shunt: *a word derived from the vocabulary of electronics; in pathology it is used to describe an anastomosis between two vascular cavities which are normally not connected.*

(4) Angiography *(from the Greek* aggeion*=vessel) is the radiography of blood vessels after the injection into them of a substance which is opaque to X-rays. This static method, which is also applied to observations made on the cavities of the heart* (angiocardiography), *has recently been perfected; today* cine-angiocardiography, *or the study of the cavities of the blood vessels and the heart in motion, is used.*

(5) *See the reference to these techniques in the next chapter, Heart Surgery by F. de Gaudart d' Allaines.*

(6) The aortic infundibulum *is a funnel-shaped region which separates the cavity of the heart (left ventricle) from the opening of the aorta.*

(7) *The intercostal arteries, subjacent to the stenosis, receive a backflow of blood from the branches of the subclavian artery above the stenosis; the aorta, downstream from the stenosis, is fed by blood which has come by abnormal diversions from upstream.*

(8) *In the embryo, the primitive single auricle is divided into the right and left auricles by a muscular wall, the* septum. *The* foramen ovale *is an opening which persists after this separation and causes the two circulations to communicate; normally it disappears after birth.*

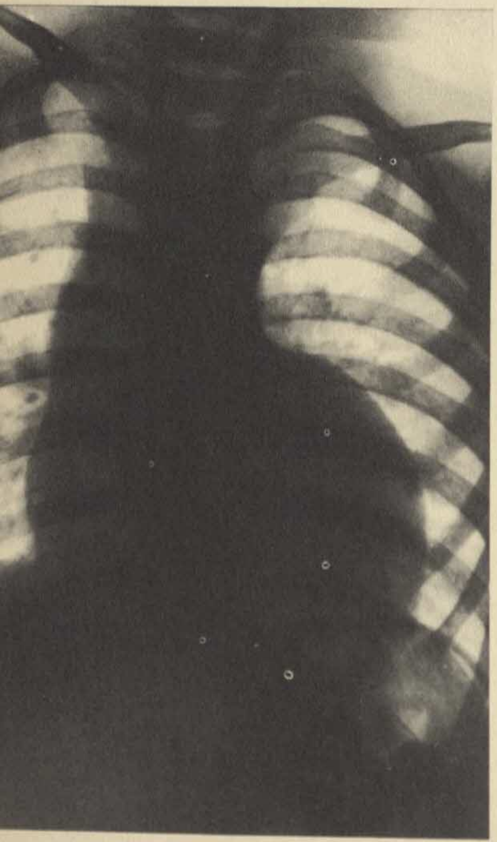

*Fig. 7. This radiograph shows the classical silhouette of the heart in blue disease—a sabot-shaped deformation and accentuated hollow of the median arch (above and to the right of the shadow of the heart) and the clear lungs. (Photo by Dr Charles Dubost).*

ance in purely interventricular communication of operating before irreversible complications have arisen.

## *Third group: malformations involving a venous-arterial shunt*

This group is characterized by a series of cadiovascular malformations which determine a venous-arterial shunt, ie, the passage of venous blood into arterial blood. This is revealed by cyanosis or blue coloration of the skin and mucous membranes.

The credit for having shed light on this problem, called the 'blue disease', belongs to Dr Antoine Fallot, of Marseilles. Before his investigations the problem was obscure.

I. The most frequent category in this group is Fallot's syndrome, so called because it comprises four conditions: stenosis of the pulmonary artery; dextraposition of the aorta; an interventricular communication; and hypertrophy of the right ventricle.

Diagnosis is based on the cyanosis, combined with deformations of the ends of the fingers into the shape of drumsticks (digital hippocratism). The physical capacity of the child is reduced and it squats down with fatigue.

The number of red blood cells is increased and radiography of the thorax shows a characteristic sabot-shaped deformation of the heart, which is accompanied by a reduction in the calibre of the pulmonary arteries.

Catheterization and angiocardiography confirm that the aorta is overriding the interventricular septum and receiving blood not only from the left ventricle but also from the right because of the stenosis of the pulmonary artery; this mixture of venous and arterial blood in the aorta is the cause of the cyanosis.

In 1944, it occurred to Helen Taussig that an anastomosis between a branch of the aorta (the subclavian artery, supplied with mixed blood) and one of the pulmonary arteries (poorly supplied with blood because of the stenosis at its origin) might have favourable results. A. Blalock performed the first operation to achieve this on a child in October, 1944. The success of the operation encouraged him to follow it up.

This historic date marks the birth of modern cardiac surgery: it not only ameliorated the condition of children afflicted with Fallot's syndrome, but also gave rise to innumerable achievements in the surgical treatment of congenital heart defects.

It was, however, only a palliative operation, which partly compensated for the consequences of many malformations inside the heart; the ideal would have been to repair these lesions completely by removing the pulmonary obstruction and closing the interventricular communications. This dream, which seemed to be unrealizable hardly ten years ago, has today become a reality. In 1954, Lillehei revealed that he had achieved the first complete correction of a Fallot syndrome by using the artificial heart-lung. We ourselves were able to report the same happy result at the end of 1956.

Today the aim that is sought is complete repair, with the heart opened, there being no more than exceptional indications for the anastomosis of Blalock.

II. The ground covered in a few years has therefore been immense, when one considers that today it is possible in a large proportion of cases to convert into ordinary human beings children who in the past would invariably have been doomed. Fallot's quadruple syndrome does not include all cases of blue disease. There is also a form, characterized by three conditions: pulmonary stenosis, interauricular communication, and an intact interventricular septum. This lesion does not lend itself to a palliative surgery: the only procedure that will lead to a cure is pulmonary valvotomy and closure of the opening between the auricles.

III. Two conditions which come into the category of cyanogenic affections but which have so far hardly led to any preparatory surgical procedure are tricuspid atresia or transpositions of the great vessels, and the existence of a common arterial trunk.

Many congenital lesions on which operations are performed may be immediately followed by the rapid appearance of a formidable complication: dissociation between the auricle and ventricle, caused by a lesion of the conducting tissue bundle (bundle of His) inside the heart, which controls the passage of the excitation of contraction from the auricles to the ventricles. The result is a marked diminution of the frequency of the ventricular contractions, the rhythm of which may, in certain cases, fall to 40 or 30 contractions per minute and cause death during syncope.

One of the most ingenious inventions of recent years is the 'pace-maker', which can transmit to the ventricle the electrical stimuli which it lacks and regulate it at the optimum rhythm.

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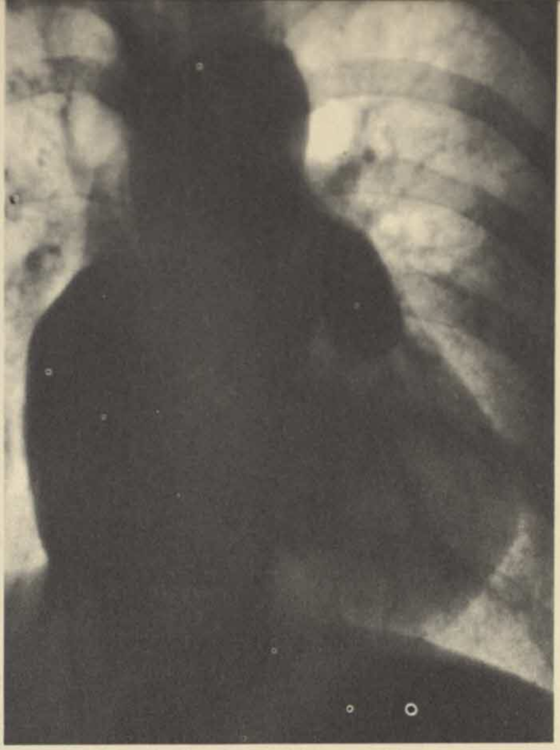
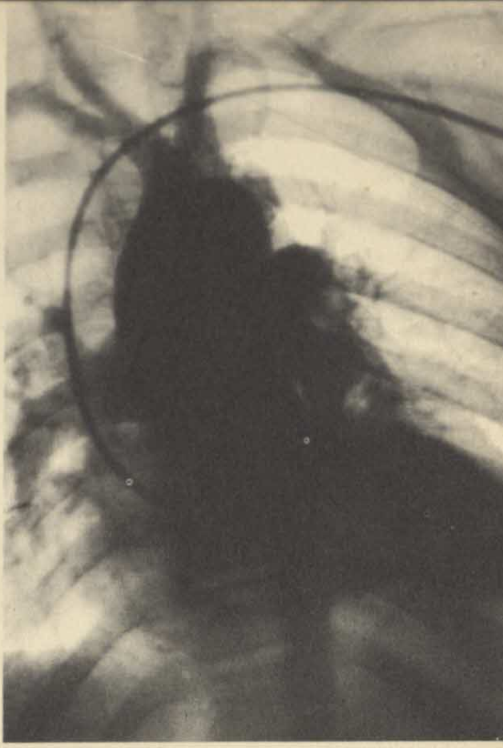
(9) *The* pulmonary arterial bed *is the name given to the mass of fine arterioles and arterial capillaries of the lung.*

(10) Interventricular septum: *the thick muscular wall which separates the two ventricles.*

*Figs. 8 and 9. Opposite, on the left, angiocardiogram of a child suffering from blue disease (Fallot's syndrome). The iodized substance injected into the circulatory system makes the voluminous aorta and the pulmonary artery simultaneously opaque. Opposite, on the right, a radiograph of a heart with an interventricular communication; the catheter, introduced through a vein in the arm, has penetrated into the left ventricle. (Photos by Dr Charles Dubost).*





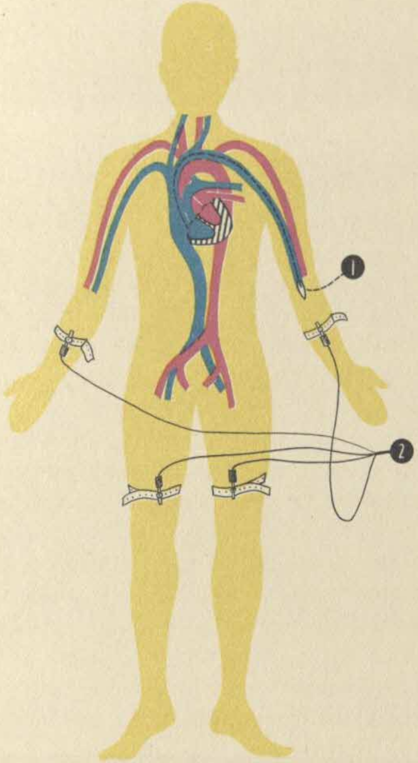


*Fig. 10. Catheterization of the cavities of the heart is an indispensable method of investigation in the diagnosis of cardiac malformations. A small, supple tube is introduced through a vein in the arm as far as the superior vena cava, the right auricle, the right ventricle, and the pulmonary artery. This makes it possible to measure the blood pressure and take samples of blood at various levels. When there is a communication between the left and right sides of the heart, the mixture of the blood is thus discovered.*

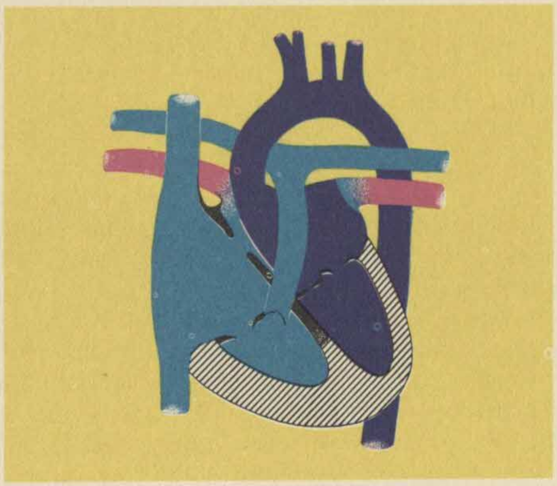


*Fig. 11. Fallot's triple syndrome, or trilogy, is a cardiovascular malformation consisting of stenosis of the pulmonary artery and a communication between the auricles. The operation for this condition enlarges the pulmonary valve and closes the foramen ovale between the two auricles. (See Fig. 10).*

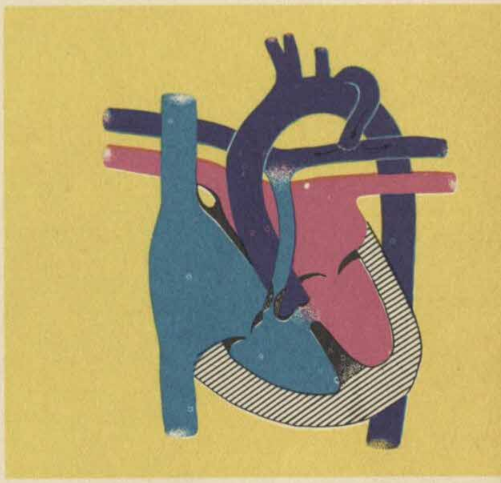
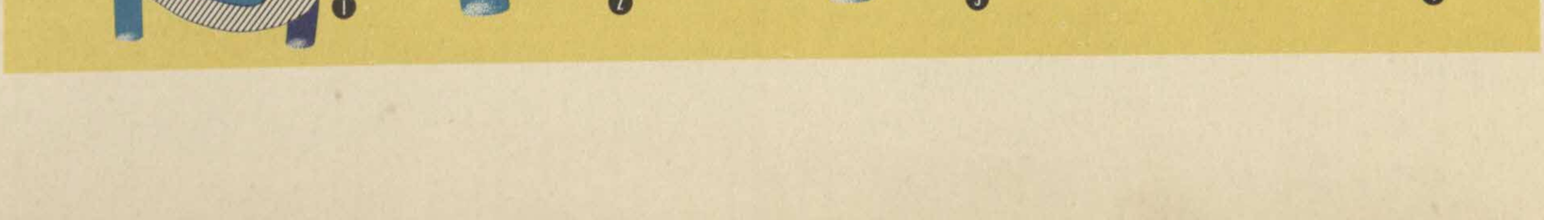


*Fig. 12. Diagram of Blalock's palliative operation for blue disease (Fallot's quadruple syndrome). This operation consists in directing to the lungs the blood they lack, sending it by way of the subclavian artery which is cut and anastomosed to the pulmonary artery.*

*Fig. 13. Modern operations for blue disease (1): the opening of the pulmonary artery is enlarged; (2) the aorta is put back in position in the left ventricle, and the interventricular communication is closed by a graft (3); the pulmonary artery is enlarged by another triangular graft (4).*



# Heart surgery.

### *François de GAUDART D'ALLAINES*

*Heart surgery constitutes an entirely new chapter in the history of medicine. The first successful operations on the heart were performed only twenty years ago, but since 1945 this branch of surgery has developed very rapidly. Its field is extending every day, owing to experimental research and new technical procedures that have begun a striking revolution in operating techniques, which have incidentally benefited other surgical disciplines far removed from cardiac surgery.*

The idea of heart surgery was mooted long before 1945, but apart from some spectacular and risky operations for suturing heart wounds, attempts at operating had ended in failure. Tuffier, Doyen and others had tried to operate on stenoses of the heart valves,[1] but the means at their disposal were inadequate and all idea of treatment by cardiac surgery was therefore set aside. These operations could not succeed with the means then available to surgeons.

Conditions changed, however, when studies began to be made of the physiological basis of anaesthetic and post-operative shock and of their consequences and the remedies for them.[2]

Modern anaesthesia has made it possible to open the two thoracic cavities without danger and to obtain perfect anaesthesia for a very long period without causing damage. Controlled observation of patients before, during and after operation has made it possible to keep them, physiologically speaking, close to normal and to prevent infection. It was this procedure that established the basis for treatment by cardiac surgery. With the publication in 1945 of accounts of their work by Alfred Blalock and Helen Taussig (Baltimore), their success immediately became known throughout the world. Their first paper stimulated research everywhere and centres for cardiac surgery were set up in England, America, Sweden, and France, and similar centres have since been set up all over the world.

It was necessary to create from scratch the conditions which would make it possible to practise cardiac surgery successfully; in a word, to establish a centre for cardiovascular surgery.

In cardiac surgery centres there are three essential requirements:

*I. Equipment*

Heart surgery aims essentially at restoring blood circulation and normal pressures in the circulatory system by correcting lesions (stenoses, leakages, etc). In a system as sensitive as the cardio-vascular system, correction of these and re-establishment of normal conditions must be as accurate as possible. The basic physiological processes must be restored and carefully controlled throughout the operation. Hence the importance of apparatus for measuring pressures inside the heart. An operation on the heart suspends or diminishes blood circulation for variable periods, and blood circulation is the carrier system for the oxygen essential to the tissues. It is necessary therefore to be able to measure diminution of oxygen (anoxia), to estimate its degree and its possible effect on various parts of the body; hence the necessity for additional apparatus, either to measure blood constants (oxygen-level, carbon dioxide content, acid-base equili-

(1) *The idea of enlarging a stenosed orifice inside the heart tempted surgeons for a long time. In 1902, Brunton attempted it in a case of mitral stenosis, but the operation was a failure. Many other surgeons afterwards tried the same thing, but also failed. In 1924, Cutler had one success in six operations; by 1930 the operation had been given up. Though it was then too serious and too uncertain, today it seems simple and harmless.*

(2) *The study of post-operative shock, the* operation disease, *and of its origin, consequences and treatment, was made by René Leriche. His work, which was important for all branches of surgery, has made it possible to perform many new operations without danger.*

brium, etc) or to observe the most sensitive organs, the brain being the most sensitive to anoxia. For this, the electroencephalogram is currently used to indicate danger to the brain from anoxia and to measure the risks of certain operative techniques. A complex assembly of instruments and apparatus supervised by a team of technicians is therefore indispensable.

*II. Surgical teams*

An operation requires several surgeons who are accustomed to working together. On their skill and co-ordination depends the smooth working of the delicate processes involved, which must sometimes be executed quickly when success or failure may be a matter of minutes. A homogeneous and well-trained surgical team is therefore essential.

Supervision of the various forms of apparatus, attention to detail, and requirements of post-operative care need technicians who are well-adapted to their work; there must also be enough of them to ensure that post-operative care is continuous.

*III. The experimental surgery laboratory*

Cardiac surgery was 'invented' after several years' research in the laboratory. It is thanks to work done there that it still progresses and that grave operational risks are avoided. The laboratory's contribution is two-fold: its purpose is to study and improve new techniques, and to accustom the surgeon to make up a team. A surgical team which has 'worked at' an operation for a long time in the experimental field passes quite naturally to the operation on man.

There are today numerous cardiovascular surgery centres where the practice of this new form of surgery, the characteristics of which are very different from those of other branches, is made possible.

Heart surgery, although it has only recently been discovered, includes a large number of varied operations; operations which last a long time and require extreme precision in their execution; operations involving physiological bases and immediate controls which need careful and continuous supervision that may need to go on without flagging for hours after the operation. For convenience, these operations are classified here in three groups, representing three types of operation and three stages in the development of this kind of surgery.

## *Surgery of congenital defects*

The first group is that which inaugurated cardiac surgery—the palliative correction of congenital defects. These defects are seen fairly often. The best-known and most striking of them is the *Fallot syndrome.*[3] This is characterized by stenosis of the pulmonary artery and by the position of the aorta, which is abnormally placed at the outlet of the right ventricle. This results in a reduction of the amount of blood passing to the lungs and insufficient oxygenation of the blood. The chronically anoxic child suffers from continual breathlessness, shows poor development and succumbs sooner or later to any complication of this condition. At the same time, the non-oxygenated blood of the right ventricle, which, because it lacks oxygen is 'blue', flows into the aorta and the peripheral circulation; this explains the cyanotic complexion of the 'blue' child.

As has been mentioned already, Blalock and Taussig were the first to conceive an operation for the cure of this condition. The principle on which the operation is based is this: following anatomical observation, the idea occurred to them of shunting the blood in the aorta into the pulmonary artery beyond the stenosis. This principle, apparently simple enough, required, in fact, many months of study, thought and experiment before Blalock was able to perform the operation. This he did by anastomosing one of the large branches of the aorta near the heart with the pulmonary artery; nowadays it is even possible to anastomose the aorta itself with the pulmonary artery (Potts', of Chicago, technique; fig. 1, A and B). Blalock's operation, made known to the world in 1946, brought about a revolution in surgical knowledge and was the start of cardiac surgery.

It is obvious, however, that this operation is not completely effective: it does not deal with the defect inside the heart but is merely palliative; it corrects the disadvantages of the defect and reduces anoxia, which was previously fatal, but it does not deal with the lesion itself. The operation is still performed, but only on patients for whom nothing better can be done.

The consequences of this operation were many. Surgeons went on to deal with congenital defects of the great vessels near the heart and quickly found a way of eliminating a patent ductus arteriosus (Gross; fig. 1, C), the communication between the aorta and the pulmonary artery, persistence of which after birth is anomalous. Gross, of Boston, and at the same time Crafoord, of Stockholm, succeeded in operating on congenital stenosis of the aorta and in securing an end-to-end suture

*A thickened and calcified mitral valve greatly magnified. (Photo Lod, by permission of Professor Kourilsky, Hôpital St Antoine, Paris).*

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(3) *Arthur Etienne Louis Fallot, of the Medical Faculty, Marseilles, discovered the anatomical lesions of the disease which bears his name in 1888. His description of it and the different varieties of it that he described are still unchanged. The principal variety of blue disease is* Fallot's syndrome, *which is characterized by the four anomalies described as: stenosis of the pulmonary artery; a communication between the two ventricles; the aorta overlapping the two ventricles; and hypertrophy of the right ventricle. The other forms of disease (Fallot's trilogy and pentalogy) are variants of it.*

of this vessel. A still more fruitful consequence was the discovery during these operations that the heart, provided it was well-oxygenated, was perfectly manageable and could tolerate manipulations and sutures without undue danger. But diseases of the heart, congenital or acquired, are inside it; hence the necessity of opening the heart in order to deal with them.

## *Operations inside the heart: mitral stenosis*

When surgeons realized that modern procedures would make it possible to penetrate inside the heart cavities, a new type of operation was studied and carried out almost simultaneously. By reviving an old idea on a new basis, Brock, of London, and Bailey, of Philadelphia, developed the operation for mitral stenosis,[4] which is now the commonest operation in cardiac surgery.

Enlargement of a mitral stenosis is achieved in the following manner: stenosis of the mitral orifice is caused by the coalescence of the anterior and posterior cusps of the mitral valve to form commissures; the cusps are more or less fused and their separation at the commissures restores normal play to the valves and abolishes the stenosis. 'Commissurotomy' is a relatively simple operation which has brought about a series of improvements in cardiac surgery. It is performed manually or with an instrument (a mitral valvotomy knife or dilator) through the inside of the left auricle which, when it is dilated, offers sufficient tissue to be opened and closed. The opening into it, usually made through a diverticulum of the auricle, permits the introduction of the finger and then, if need be, the instrument. It is necessary to dilate the orifice sufficiently, but not too much, taking into account the possibility of other cardiac affections and modifications in the walls and cavities of the heart. Because of this, the practice has arisen of physiological measurement of the pressures inside the heart during an operation. Thus, by means of measuring instruments, the surgeon is able to estimate the work he has done and how much remains for him to do.

The frequent performance of this operation has enabled a fuller study to be made of the sequels to operations on the heart, and their possible complications, as well as of methods of treatment. Intracardiac thromboses (coagulations), which cause embolisms, and cardiac reflexes arising from interference with the rich nervous tissue inside and outside the heart, have been studied and defined, and precise rules have been formulated for their prevention. The gravity of these operations has diminished considerably and their results have improved.

## *Open-heart operations*

The operation for mitral stenosis (valvotomy) led surgeons to use a more daring technique. In this case the operation is performed by touch, without the surgeon being able to see what he is doing. But, of course, an operation is best performed when he can see exactly what is taking place. The problem, therefore, was how to open the heart and interrupt the circulation in order to be able to have a clear view of what was happening. After some years of study, the technique of open-heart surgery has now been elaborated.

To open the heart it is necessary to empty out the blood inside it and so arrest the circulation; but arrest of the circulation stops the supply of oxygen to the tissues. Acute anoxia causes fatal lesions of the two most sensitive organs, the brain and the heart, within three minutes. But this is not long enough to perform an operation. It is therefore necessary either to prolong the operation or to arrange artificial irrigation of the brain and of the walls of the heart, while the cavities of the heart are completely emptied of blood. Two methods are used.

*Cooling of the body (hypothermia)* which increases its tolerance of anoxia and makes it possible to arrest the circulation for a longer time (Bigelow, Swann; fig. 2).

Oxygen is used by the cells of the body to maintain metabolism. By bringing down the patient's temperature, metabolism can be lowered and the need for oxygen thus diminished.

Acute anoxia causes irreversible cellular lesions in three minutes at normal body temperature. By lowering the temperature to about 30°C, a period of six or seven minutes is available for carrying out certain rapid operations inside the heart. The commonest of these is closure of communication between the two auricles. The anaesthetized patient is brought to a temperature of about 30°C. Six minutes is long enough in which to arrest the blood circulation at the heart entry, to open the heart, and to close the abnormal communication.[5]

Moderate hypothermia is a relatively easy

(4) Mitral stenosis *which is usually due to a rheumatic infection, consists of a progressive closure of the mitral ring which joins the left auricle to the left ventricle. The mechanical consequences lead to serious and progressive conditions ending in fatal complications. The blood is retained in the left auricle which is dilated, and the stasis of the blood then reaches the lung and subsequently the right side of the heart, the walls of whose cavities hypertrophy; the cavities then become dilated until right-sided heart failure occurs, which in course of time is fatal.*

(5) *It would seem logical to lower the temperature below 30° to increase the time allowed for the operation. Until not long ago, serious disturbances (fibrillation) of the rhythm of the heart made it impossible to lower the temperature any further because of the risk of irreversibly arresting the heart. Today, it is possible to use deep hypothermia (12°C).*

(6) *An exact diagnosis is essential for performing an operation inside the heart. The surgeon must know which cavity to open and the importance of what he will find to repair. Pre-operative diagnosis is sometimes insufficient. The surgeon's first action is therefore to employ 'the intracardiac touch' by introducing a finger through a small incision into one auricle, so as to be able to form an estimate of the lesions. This is the moment at which he decides on the plan and method of the operation.*

technique. Its use, however, is limited to the treatment of lesions of which the diagnosis is certain and the operative cure rapid.

Most lesions inside the heart are too complex or too problematical for it to be possible to repair them in five or six minutes. In such cases it is therefore necessary to use another method.[6]

## *Extracorporeal circulation: the artificial heart-lung*

This method, the fruit of many years' work and innumerable experiments, is now perfected and in general use.

To open the heart wide when it is empty of blood, and at the same time to keep up the blood supply to the body to give it the necessary oxygen, involves the creation of an extracorporeal circulation. This is done by removing the venous blood as it reaches the heart through the two venae cavae and returning the blood to the arterial circulation where this leaves the heart; this means that both heart and lungs are out of circuit, so a motor is used to ensure circulation outside the body, acting as an artificial heart; during this process the blood must be oxygenated, and for this purpose an artificial lung is used (fig. 3).

The mechanical problem of this artificial heart is relatively simple, but the biological problem of oxygenation of the blood by an artificial lung is extremely complex.[7] It is due to the heart-lung that the surgeon is able to perform all the principal major operations of intracardiac surgery. The heart can be widely opened and operated upon without haste; in fact, periods of three-quarters of an hour to an hour are currently used. During these operations, supervision of the machine and the patient's reactions must be scrupulously careful and continuous. The various forms of apparatus in use make it possible to follow temperature and humoural changes in the body-fluids and to detect at once any danger of anoxia.

The artificial heart-lung makes it possible to operate nowadays on such complex congenital defects as those of Fallot's syndrome and of the various communications between the cavities of the heart. Little by little, cures are being found for stenoses of the aortic orifice and diseases of the coronary arteries, especially atherosclerosis.

## *Induced cardiac arrest*

It might well seem that the artificial

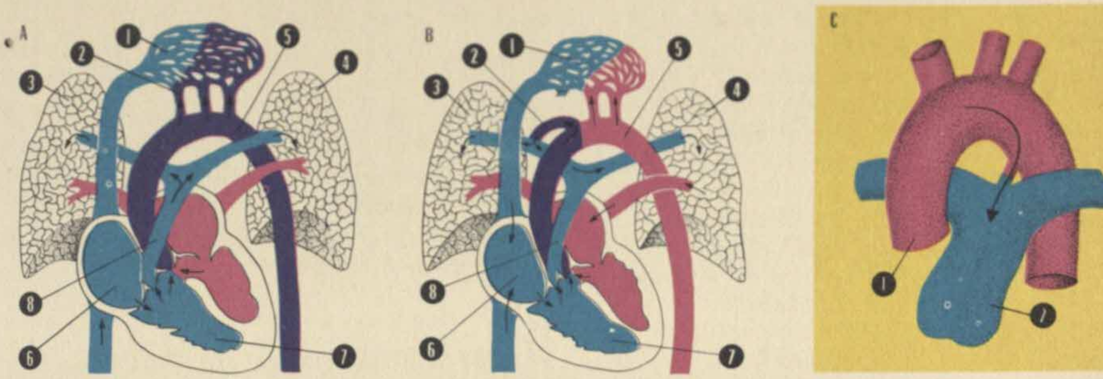

*Fig. 1. A and B—Fallot's quadruple syndrome or blue disease, characterized by specific anatomical lesions: stenosis of the pulmonary artery at its base and communication between the ventricles. A: before operation, the blood which enters the aorta (5) is mixed with venous blood, hence the blue colour of the skin. B: diagram of the first operation for blue disease performed by A. Blalock and H. Taussig in 1944. A branch of the aorta, the subclavian (2), is anastomosed with the right-hand branch of the pulmonary artery; in this way part of the venous blood is sent to the lungs, where it is oxygenated. 1, circulation in the head and the upper limbs; 2, subclavian artery; 3, right lung; 4, left lung; 5, aorta; 6, right auricle; 7, right ventricle; 8, pulmonary artery. C: persistence of the ductus arteriosus. This communication between the aorta and the pulmonary artery is a survival of embryonic conditions; normally the ductus arteriosus is destroyed at birth.*

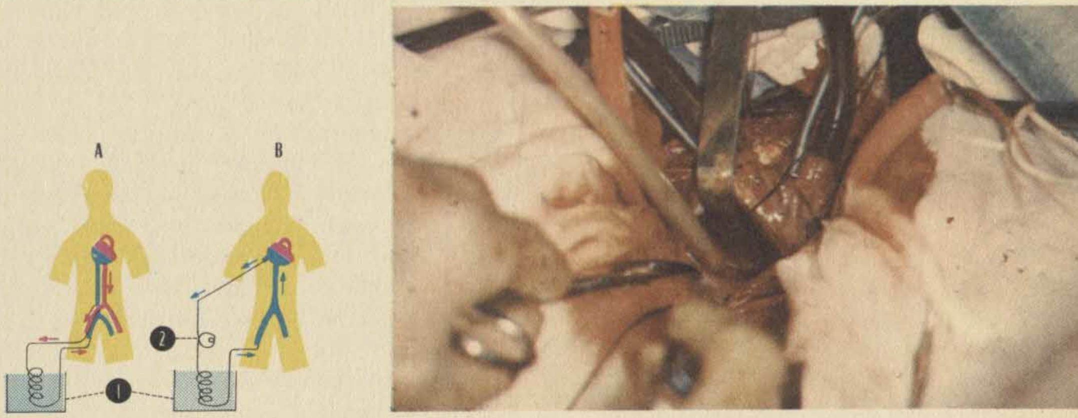

*Fig. 2. On the left, a diagram representing two methods of refrigerating a patient for operations under hypothermia; the blood passes into a refrigerator and returns into the circulation: A. artery-to-vein method; B. vein-to-vein method; 1, cooling tank; 2, pump.*

*On the right, an operation on the open heart under hypothermia; a communication between the auricles is being closed; the probe below and the retractor above are in the communicating opening. The operation can be performed in a few minutes. (Photo by Dr Jean Waysse).*

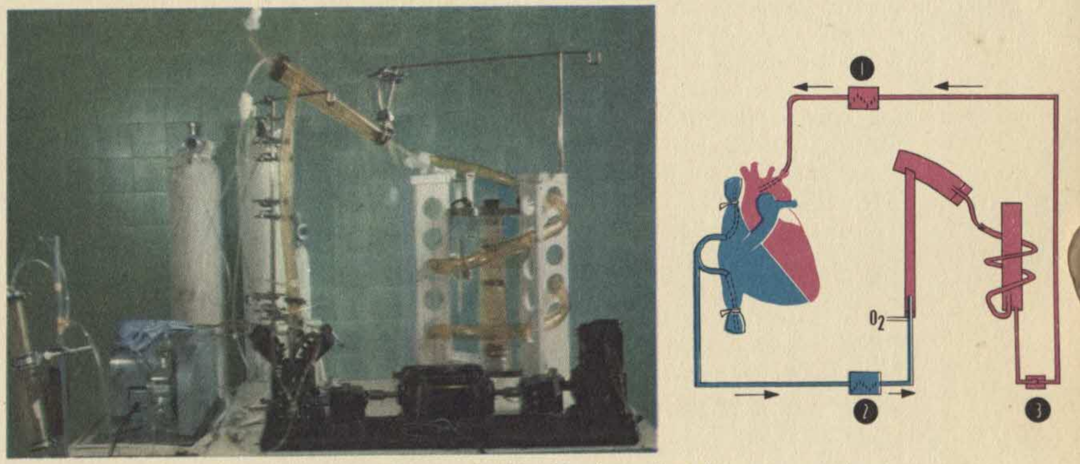

*Fig. 3. On the left, Dewall's artificial heart-lung. Below on the right of the photograph are the motors; one sucks out the venous blood, the other drives the oxygenated blood back into the aorta. On the right, the oxygenator; on the left a reservoir (for storage of the oxygenated blood before its recovery). (Photo by Dr Waysse). On the right, a simplified diagram of the same heart-lung; the blood is taken from the two venae cavae before its entry into the cavities of the heart; the oxygenated blood is sent back to the arch of the aorta; the heart and the lungs are thus out of circuit. 1, arterial pump; 2, venous pump; 3, filter.*

heart-lung represents the apotheosis of progress in cardiac surgery. In fact, there is» something even more remarkable. Opening the cavities of the heart makes it possible to have a good view of the lesions, but ideal surgical technique requires that in this case, as in many other branches of surgery, two conditions be met: (1) an immobilized organ, which is (2) drained of the blood which normally circulates through it. This is required for the repair of complex and deeply-situated lesions, for which it is essential to keep the heart still.

Arrest of the heart can be brought about in three ways: *(a)* drug-induced arrest: a substance injected into the coronary arteries[8] temporarily paralyses the heart muscle; when this substance has been eliminated after the operation, the heart starts again; *(b)* anoxic arrest, achieved by the suspension of all circulation in the heart walls, which causes a momentary arrest of its contractions. These two methods make possible stoppages of short duration; *(c)* a third method, more recent and coming more into use, makes possible a more prolonged arrest of up to forty-five minutes; the arrest can be repeated if necessary.

This method combines extracorporeal circulation and cold. We have seen above[5] that it is dangerous to lower the temperature below 30°C. But if there is an extracorporeal circulation, it can be reduced to 12°C and perhaps even lower without danger. At this temperature, metabolism is lowered by 90 per cent; life is so much slowed down that it hardly exists at all, and consequently the oxygen reserves of the organism are sufficient for the heart to withstand prolonged arrest.

The technique is as follows: the blood which is circulating in the artificial heart-lung is cooled in the course of its circulation. The patient's temperature is lowered and the heart progressively stops until electric, electrocardiographic and electroencephalographic data register an almost complete suspension of life. At this moment, no artificial circulation is needed; the cell metabolism is so much lowered that the body no longer requires any oxygen and the operation proceeds easily on a cold, motionless and apparently dead heart, which can, however, be re-started when the artificial heart-lung is once more put into action and circulates blood that has again been warmed.

Thanks to this method, the most delicate operations in the depths of the heart cavities (the techniques of Drew and Dubost) are carried out with the maximum of ease.

## *Electrical pacing of the heart*

The contraction of the heart muscle takes place in succession from the auricles to the ventricles. The harmonious succession of heart contractions is governed by a conducting tissue (bundle of His), which ensures that the contractions are rhythmical and co-ordinated. But during an operation, the bundle may be injured, an unforeseeable accident because the bundle is invisible to the naked eye and sometimes lies in an abnormal position.

The result of injury to it results in arythmical unco-ordinated contractions of the auricles and ventricles (auriculo-ventricular block); the auricle no longer sets the pace for the ventricle and the latter ends by going into a state of arrest. This is a grave complication which is sometimes fatal in a few hours.

In serious cases that cannot be cured by medical treatment, two electrodes are introduced which are connected to an electric battery and cause a contraction of the ventricle at each contraction of the auricle. This instrument, known as a pace-maker, makes it possible to maintain contractions of the ventricle which are of normal vigour and rhythm until a return of the natural function.

In spite of considerable progress, heart surgery still has a large sphere to explore. Everything that hinders automatic function belongs in principle to the domain of surgery. Meanwhile, there are a number of cardiac diseases that still cannot be cured; nevertheless, the problems presented by these diseases are being tackled by experimental research laboratories. We know, for instance, how to enlarge a stenosed orifice and how to close an abnormal channel, but when the tissues are too much affected and too much enfeebled by disease their simple repair is not a complete answer. In such cases, it is necessary to consider the use of grafts of organs[9], or of plastics which are used to form tubes or inert plates. But modern research is aimed at finding a way of using complete mobile valves to replace a part of the heart that is too diseased to be repaired. Research is also being directed to finding a means of replacing the whole heart by an artificial one placed in the thorax and operated electrically (Kolff). So far, these procedures are purely experimental, their results are not yet complete, and they are still unusable; but it does seem that the development of surgical techniques, which has been so spectacular and so rapid, is opening up new possibilities whose practical application may be close at hand.

(7) *Artificial oxygenation of the blood must reproduce the biological process of liberation of the* $CO_2$ *of the circulating blood and the fixation of the oxygen. This is a difficult problem. There are numerous types of artificial lung; they fall into three groups:* (a) *mixing, by bubbling oxygen through the blood (Lilehei-Dewall's apparatus);* (b) *distribution of the blood over smooth surfaces in contact with oxygen (Gibbon's, Key's, Cross's apparatuses, etc);* (c) *the passage of dissolved oxygen through a filter membrane analogous to the pulmonary membrane (Thomas's apparatus).*

(8) *The drug generally used is potassium citrate, which arrests the contractions of the heart muscle. The drug is introduced into the coronary arteries and all circulation at this level is blocked (clamping of the aorta), so that the drug will remain in place. At the end of the operation, the circulation is freed again and the drug is eliminated by the blood which again circulates. The heart-beats return.*

(9) *Grafts for replacing an artery that is diseased, even over a very long part of its course, are today commonly used with very good results. Either preserved human grafts are used, or synthetic grafts of nylon, dacron, etc. In intracardiac surgery plaques made of ivalon are used to close an abnormal opening of large size.*

# Surgery of the autonomic nervous system and vascular surgery

*Jean KUNLIN*

It was the anatomist, J. B. Winslow who, in 1732, introduced the term 'sympathetic' to designate the nerves which control the 'sympathies', as they were then called; that is to say, the reciprocal relations between the organs of the body. About 1800, Ernest Bichat called them the nerves of 'vegetative life', because they functioned in an unconscious and involuntary way, in contrast to the motor and sensory nerves of 'animal life', the activity of which is conscious and under the control of the will. The autonomic nervous system was located by Bichat solely in the long sympathetic nerve passing down the anterior surface of the vertebral column.

## *The autonomic nervous system*

Later on, physiologists demonstrated the existence of other autonomic nerves which are connected to certain cranial or spinal nerves and are grouped under the name parasympathetic. For a long time sympathetic and parasympathetic were contrasted because their essential functions are often opposed to each other; thus, for example, electrical excitation of the sympathetic fibres leading to the heart accelerates heart-beat, while excitation of the parasympathetic nerves slows it down. Actually, the two form an interdependent whole combined under the name of autonomic nervous system, of which there are three parts:

I. The nerve centres—those for the sympathetic being distinct from, but near to, those for the parasympathetic system—are situated at the base of the brain in the medulla and spinal cord; they consist of nerve cells, prolongations of which form fibres which connect with secondary centres outside the cerebrospinal column. These secondary centres in their turn send nerves to the various areas in which they are distributed.

II. The main sympathetic nerve chain (which is a relay, or secondary, centre) is formed by a nerve with enlargements at intervals, called ganglia, which contain nerve cells. The ganglia are connected with the cerebrospinal centres and send out nerves to the organs, the blood vessels and the skin.

III. The parasympathetic is made up of two groups of nerve fibres: (1) the cranial parasympathetic fibres; these come from the cerebral centres at the base of the brain and accompany certain cranial nerves for part of their course, then detach themselves to end in the ganglion relays, from which other fibres go to the organs; (2) the sacral parasympathetic fibres, which come from centres in the lower spinal cord and detach themselves from the sacral nerves and come into relation, through intermediary ganglion relays, with organs in the pelvis.

The autonomic nervous system also contains centripetal fibres; that is to say, sensory fibres, which provide information about the functioning of an organ and initiate corrective reflexes. Sometimes this system produces painful sensations, which are conscious and transmitted either by sympathetic or parasympathetic fibres.

The autonomic nervous system is symmetrical: there is a right and a left system and these are extensively interconnected, especially in relation to the main organs. The system comes under the influence of the cerebral cortex, sometimes with harmful results. The system plays an important part in the harmonious regulation of the functioning of the organs and other parts of the body—general or local circulation, blood pressure, respiration, digestion, glandular secretions, sweating, temperature, etc—and consequently takes part in all reactions of the organism to disease.

It was René Leriche especially who, after Jaboulay's earlier efforts, considerably developed surgery of the autonomic nervous system. Removal of the nerves which surround an artery (periarterial sympathectomy) improves the circulation in the area which it supplies. Removal of the ganglia of the sympathetic chain has a more marked and more lasting effect. Leriche tried to modify the progress of certain chronic diseases by operating on nerves of the autonomic system, either by cutting the secretory nerves to certain glands in order to diminish their harmful activity, or by cutting the sympathetic nerves in order to

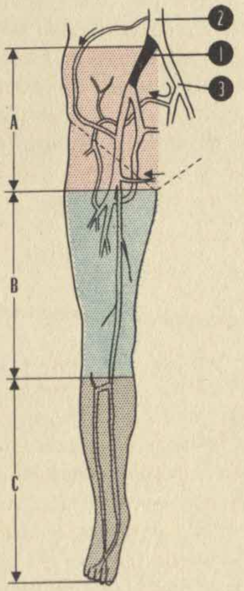

*Fig. 1. The obstruction (thrombosis, embolus) of a large artery in one of the lower limbs is often followed by very severe symptoms (coldness and gangrene). 1. obstruction; 2, common abdominal aorta; 3, iliac artery. In A, in spite of the obstructions, circulation is satisfactory owing to the collateral vessels. In B, the circulation is insufficient for walking. In C, it is insufficient even at rest.*

increase the activity of these glands and improve circulation. These attempts have not always given the results that were hoped for. But Leriche was a pioneer and showed the way. The operations most often practised on the autonomic nervous system are: removal of sympathetic ganglia for circulatory disturbances which are spasmodic (Adson) or due to arteritis, or excessive sweating of the extremities; extensive thoracico-lumbar sympathectomy for certain forms of hypertension; and resection of the presacral nerve, a branch of the lumbar sympathetic nerve, for painful disturbances of the pelvis (Cotte). As regards the parasympathetic system, the vagus or pneumogastric nerve is cut with the object of diminishing increased secretion of gastric juice (Dragstedt).

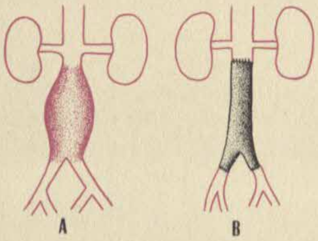

*Fig. 2. A, fusiform aneurysm of the inferior abdominal aorta. B, the same aorta after resection and insertion of a graft.*

## Arterial emboli

The first operations aimed at producing a vasodilator effect (arteritis of the lower limbs, for example) were performed on the sympathetic nervous system, but the progress of surgery and resuscitation and new techniques of arteriography made it possible to diagnose and locate thrombosis and to try to operate on it without danger. The possibility of using vascular grafts has transformed this surgery of the blood vessels.

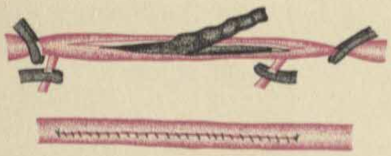

*Fig. 3. An obstruction of not more than a few centimetres can be dealt with by clearing the lumen of the artery, withdrawing the clot, and then suturing the vessel.*

When a clot fragment is detached from the wall of an aneurysm or from the cavity of a heart affected by certain forms of disease, it is carried away by the bloodstream and then brought to a stop at the place where the diameter of the artery, which decreases along its length, prevents it from going any further. Depending on the point of its arrest, the embolus[1] may cause serious disturbances by arresting the arterial circulation; if it lodges in the carotid artery, this may lead to hemiplegia, if in the abdomen, to gangrene of the intestine, or if in the limbs, to necrosis of the extremities.

It is therefore necessary in such cases to operate as soon as possible, by incising the artery at the site of the embolus if it is accessible, withdrawing the clot, and suturing the vessel. The condition of the patient with cardiac disease does not always allow this operation, but there are methods, already mentioned, of slowly improving a deficient circulation. In order to avoid a relapse, it is also necessary to consider surgical treatment of the cause of the embolism: ie, disease of the heart or an aneurysm (fig. 2).

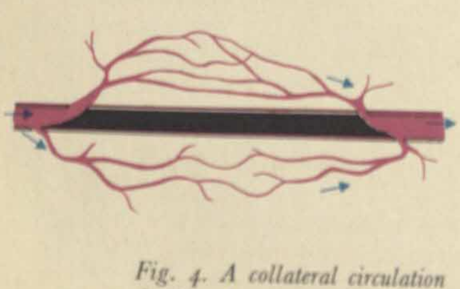

*Fig. 4. A collateral circulation develops between the two parts of an artery obstructed by a clot.*

Forms of arteritis which obliterate vessels are due, as spontaneous aneurysms often are, to a general disease in which the part played by fats, and especially cholesterol, is imperfectly understood. In other cases calcifications are found in arteries, or arteries that are abnormally narrow for young people.

The disease usually reveals itself only when the lumen of the artery is very much narrowed or when it is blocked by a clot (thrombosis). Massive obliteration of a large artery may be followed by very severe manifestations: for example, in the lower limbs, which are very often affected, pallor, lowering of temperature, numbness and then gangrene (fig. 1). But often the disease reveals itself only when an effort is made (intermittent occlusion).

Treatment for arteritis should always be medical, but sometimes surgical treatment is also needed. Until a means of preventing the disease has been found, the treatment must continue to be a diet low in fats, drugs to stimulate the liver, and vasodilators and anticoagulants. Studies are being made of fibrinolytic drugs with the object of producing a drug which can dissolve the clot. Among the vasodilator methods most effective in restoring the limb are surgical removal of certain sympathetic ganglia, or in cases of arteritis in young people, removal of the suprarenal glands, either unilaterally (V. Oppel) or, in severe cases, bilaterally and partially.

All diseases of arteries involve a common risk: that of slowing down the circulation in the areas supplied by them. This ischaemia[2] is due to the occlusion of the artery by a clot formed locally (thrombosis) (fig. 3), or by a clot brought by the blood-stream which sets up an arterial embolus, or by an operation on an artery for the treatment of a lesion (ligature, total or partial resection). In a case such as this, gangrene, which is caused by lack of circulation, does not necessarily occur, because a small amount of blood, which is carried by collateral vessels that branch from the principal one above the obstruction, infiltrates by diversions to the peripheral tissues, bringing them enough oxygen and nutritive materials to enable them to survive. But when an effort is called for, these badly-nourished tissues cannot provide it and suffer accordingly. Thus a brain that is poorly supplied with blood is easily fatigued by intellectual work; climbing will cause a pain in the heart or cramp in the calf of the leg, causing the patient to stop (intermittent occlusion).

The organism is capable of compensating slowly for these disturbances: the collateral vessels become enlarged (fig. 4), bringing more blood to the area dependent on the

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(1) Embolus: *a clot or some other kind of plug brought by the blood from a larger to a smaller vessel, causing obstruction of the latter.*

(2) Ischaemia: *a local and temporary deficiency of blood, due chiefly to the contraction or obstruction of a vessel.*

obstructed artery, but this happens only on condition that no new occlusion occurs. Nevertheless, there are, even at rest, critical painful stages and attempts to ameliorate these must be made as soon as possible. How can this be done?

The drugs most used are the vasodilators taken orally or by subcutaneous or intramuscular injection; but their action is more powerful when they are introduced into the artery at a point just above the obstruction (intra-arterial injection). Another method is to block the vasoconstrictor sympathetic nerves with an anaesthetic, the drug being introduced either in contact with the vasculo-nervous pedicle leading towards the area that is poorly supplied with blood, or with the sympathetic ganglia from which the vasoconstrictor nerves come (Leriche's infiltrations). In spite of the very transient effect of the anaesthetic, improvement often persists in the affected region. Leriche attributed this to the suppression of vasoconstrictor reflexes resulting from a ligature or from the arterial lesion.

In arterial diseases which cause thrombosis it is also necessary to use such anticoagulants as herapin or antivitamin K (a derivative of coumarin). Studies are now in progress on fibrinolytic drugs aimed at dissolving the clot.

## *Surgery of arteries and arterial wounds*

Surgery, especially sympathectomy, can appreciably improve the condition of a limb or an area that is poorly supplied with blood. But grafting, when this method can be used, which is not always the case, is the best means of re-establishing the circulation; indeed it can bring about the disappearance of all clinical signs of the disease.

The arterial graft, whether combined with thrombectomy or not, sometimes makes it possible to bring sufficient blood to the extremities and to avoid gangrene where this operation would have seemed impossible a short time ago.

Modern surgery of arteries and veins has become possible because of numerous technical improvements. Progress in anaesthetics, antiseptics, and antibiotics, a more precise knowledge of the disturbances that follow every surgical operation (Leriche's post-operative signs), and measures to correct these troubles are the foundations on which modern vascular surgery have been established.

Instrumentation has also been improved. It is only a hundred years ago that Koeberlé and Péan invented haemostatic forceps. New instruments have since been invented which are more practical and do less damage: forceps which make it possible to compress between thin limbs the most fragile as well as the largest blood vessels, the aorta, for instance, without injuring them and without slipping; fine needles which are strong and have the suture thread inserted at their bases (non-traumatic needles); needle-holders with tungsten or diamond grips firmly hold the needle in whatever position is chosen.

The first arterial grafts for treating traumatic aneurysms (fig. 5) of the limbs (Goyanes, Lexer) were made at the beginning of the century; this, the only true graft, was done by using a vein taken from the patient (fig. 6). The operation was seldom performed. Since 1948, as a result of work done in Boston and in Paris, grafting has been used more often to rid the organism of certain congenital malformations of the arteries, including the larger ones. Shortly before that time a new technique for clearing arterial obstructions was tried out in Lisbon. Some surgeons used a patient's vein, others an artery taken asceptically from a fresh corpse and preserved in a suitable medium in a refrigerator (artery bank). Then came the supple woven or knitted plastic tube (made of dacron or teflon) which is well tolerated by the organism. The fine porous wall of this artificial graft makes good fixation possible. Its inner surface becomes coated by the circulating blood with a fine coagulum of fibrin which progressively gives place to a smooth connective tissue membrane curiously like the internal lining of an artery.

Wounds of the large arteries of the trunk are very serious, but not always fatal if the wound is small. On the other hand, the arteries of the limbs are very contractile and, thanks to this property and to the vasoconstrictor functions of the sympathetic nervous system, the fall in the arterial pressure and the coagulation of the blood, bleeding may stop entirely and spontaneously, even when an artery has been completely severed. After compression of the artery or application of a tourniquet (which must not be left on for longer than three to four hours) the surgeon will clean up the wound and apply the necessary ligatures. The modern tendency is to aim at re-establishing the continuity of the artery by sutures (fig. 7) if the wound is clean-cut, or by a graft if there has been a loss of substance. Even in the surgery of war-wounds this practice tends to supplant ligaturing methods, especially if the

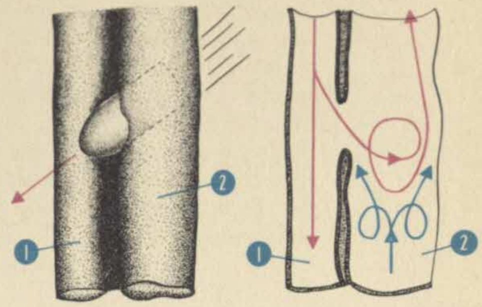


*Fig. 5. A traumatic aneurysm caused by a bullet which has simultaneously wounded a vein and an artery. Arterial blood passes directly into the vein and returns to the heart.*

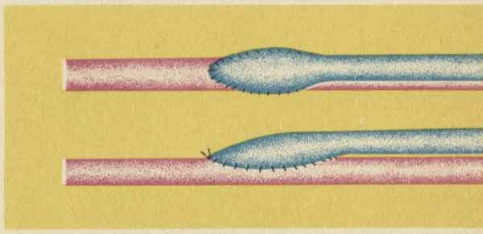


*Fig. 6. Anterior and lateral views of a by-pass graft made by grafting a vein on to an artery of medium calibre.*

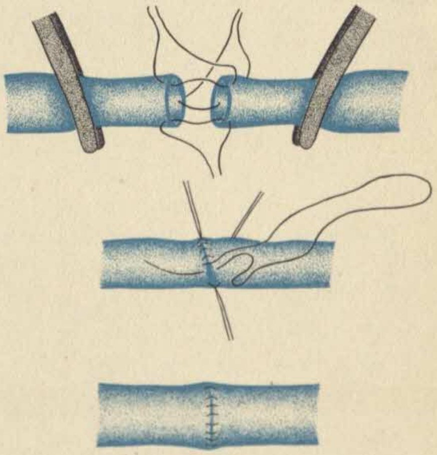
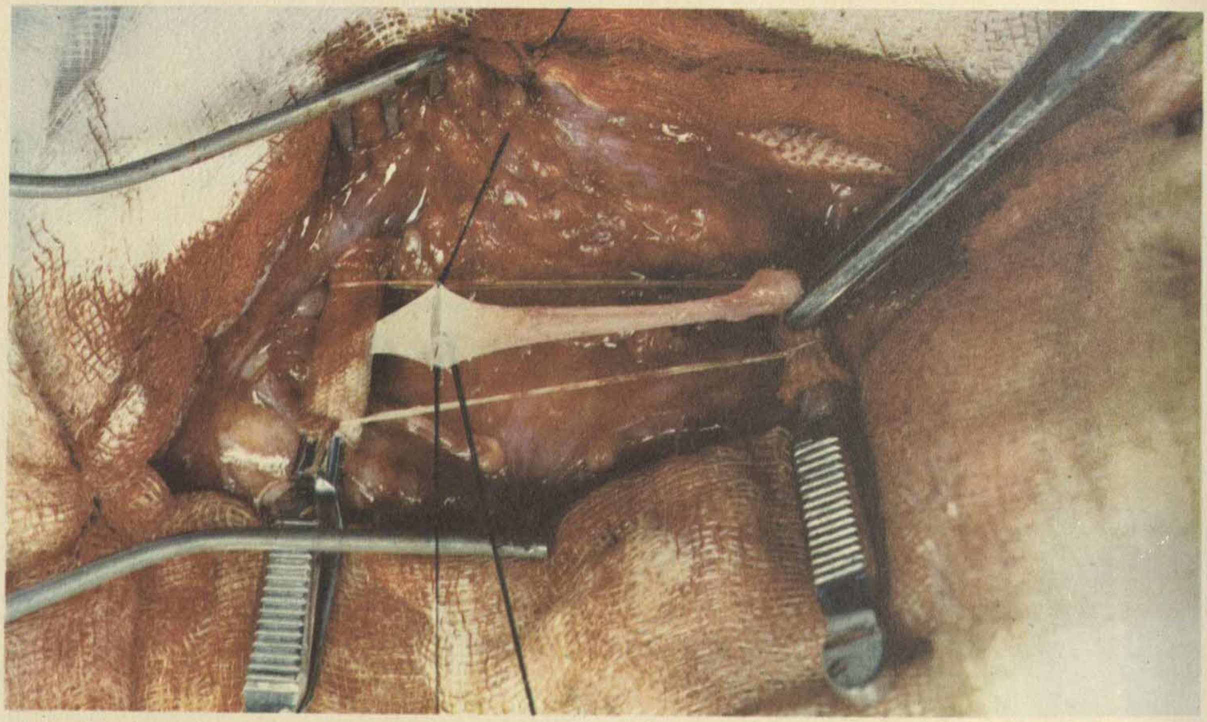


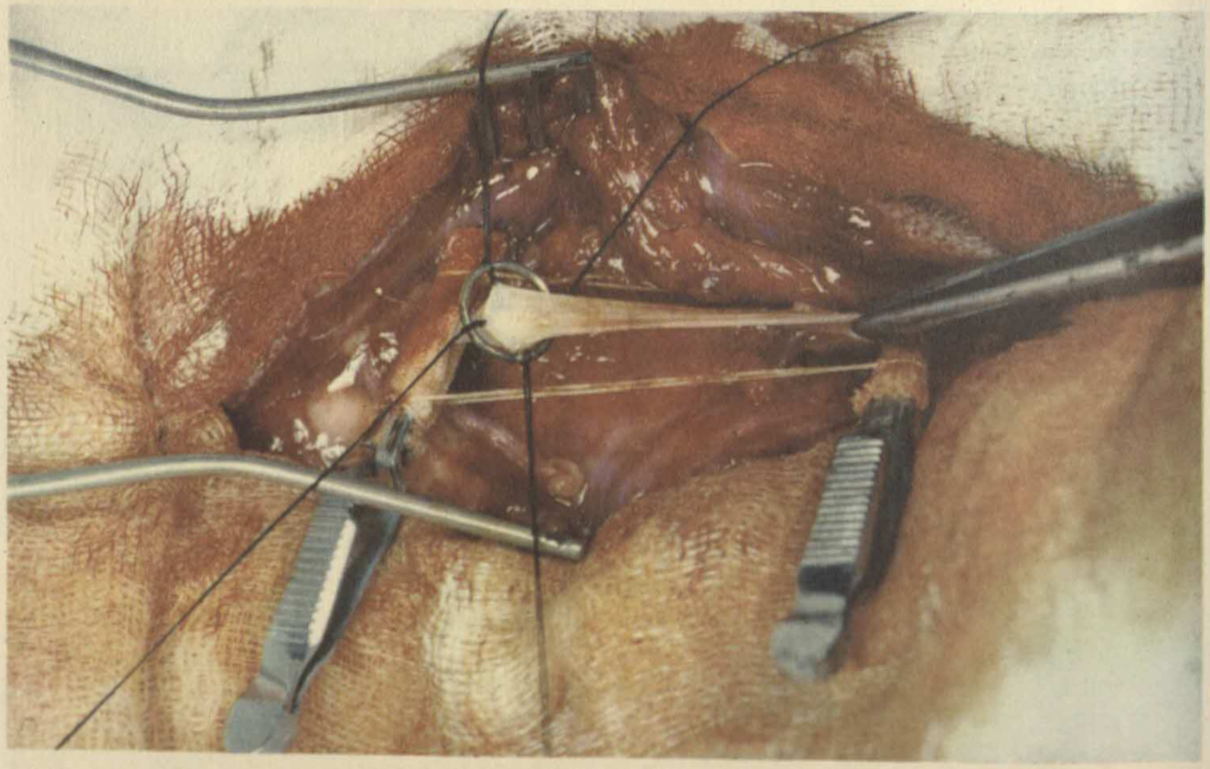
*Fig. 7. End-to-end suture of a blood vessel by Carrel's method. After preparation of the two ends, the two parts are sutured by a simple overcast stitch.*

# *Suspended suture*

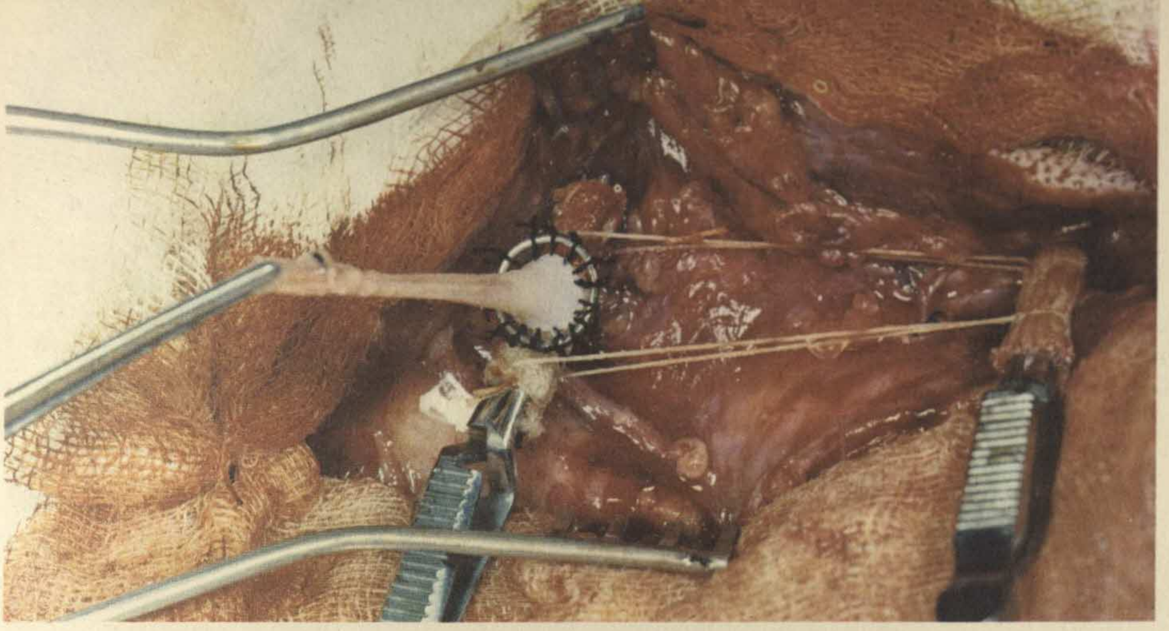
*In the surgery of veins, certain difficulties are encountered because low venous pressure does not allow the wall of the vessel to counteract the contraction of the scar, and a stenosis of the diameter of the vein often forms at the point of union. A new technique, that of the suspended suture, makes it possible to overcome this difficulty and to carry out venous grafts under the best conditions. (Photo Lod).*



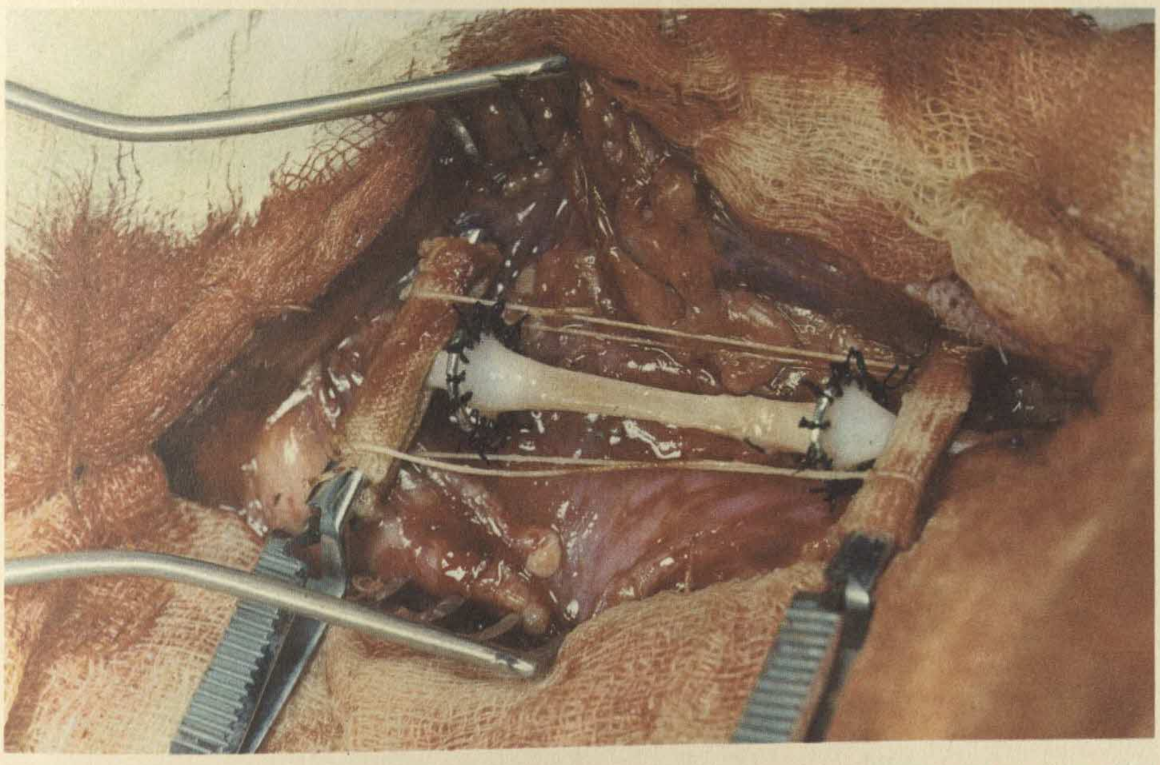
*The graft (the white, horizontal band in the middle of the illustration) is put into position at the end of the vein by two sutures and is kept in a state of tension by forceps (on the right). The two ends of the vein are clamped by two small pairs of forceps covered with a sheath of cotton which prevents them from slipping.*



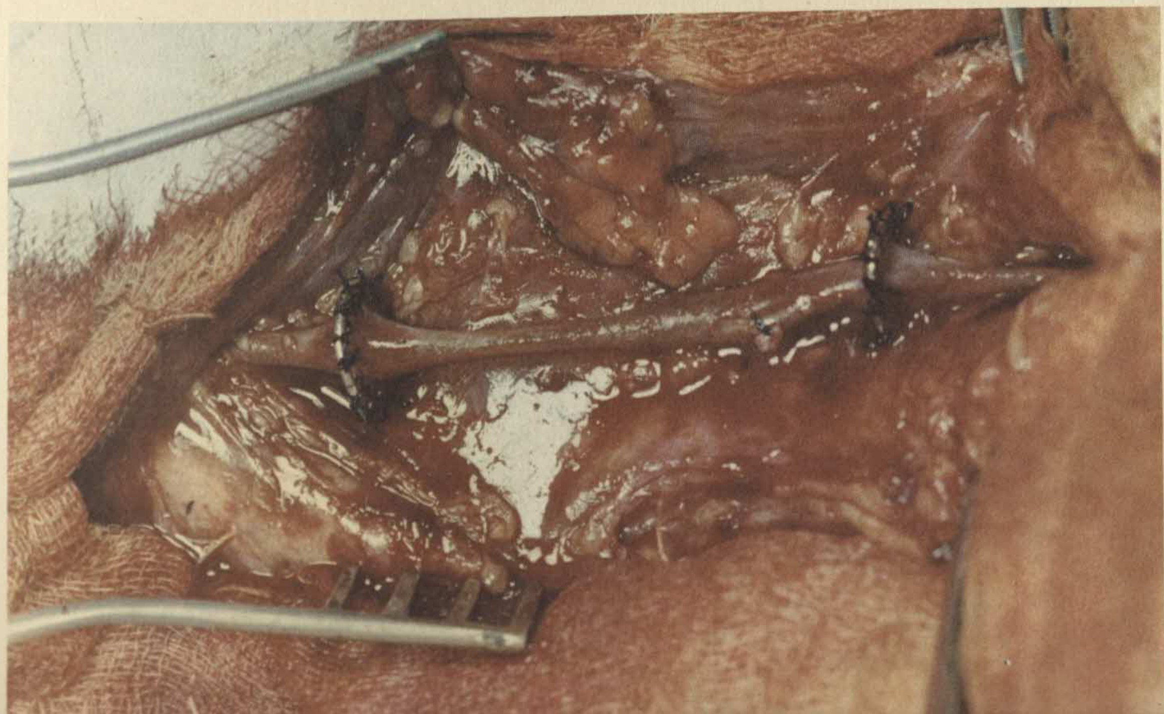
*The graft is joined to the vein by four equidistant sutures. These are tied on to an inoxidizable metal ring: this keeps open the region of the junction between the vein and the graft.*



*The intermediate sutures are put in and these are then in their turn tied to the metal ring. The suture resembles a snow-shoe.*



*The other end of the graft is fixed by the same technique and the operation is finished, leaving the two rings in position.*



*The two pairs of cotton-sheathed forceps are withdrawn and circulation is re-established. There is slight haemorrhage until the fibrin of the blood is distributed uniformly over the internal wall of the graft and at the suture points and makes these impermeable. The wound is then closed.*

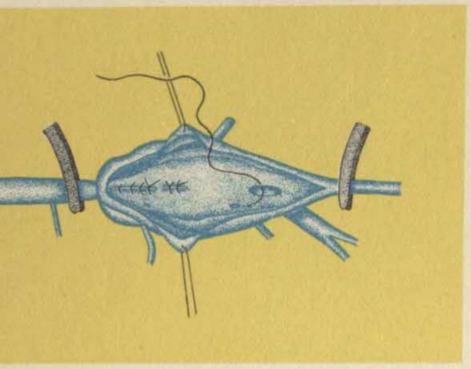


*Fig. 8. Matas's operation, used for aneurysms of the limbs. The aneurysm sac is opened and the internal opening is then closed with a suture.*

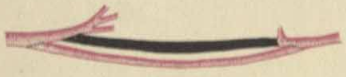


*Fig. 9. The* by-pass graft *is a technique that is coming increasingly into use. When it is not possible to suture or clear away an obstruction, the graft is joined laterally to the vessel at two places.*

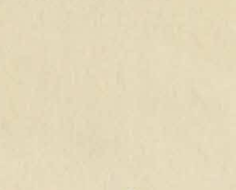


*Fig. 10. A suspended suture of a vein: the separate stitches of the suture are tied to an inoxidizable metal ring. The region of the junction of the two ends is kept wide open; the collapse of the vessel, which is the chief cause of failures, is thus avoided.*

wound is at a point where the tying of the artery would involve the risk of causing a serious slowing up of the peripheral circulation (for example, the popliteal artery in the knee).

## *Spontaneous aneurysms*

An arterial wound may bleed relatively little and under certain conditions the bleeding may be confined to a limited space. A haematoma is then formed, which is composed largely of clots which prevent a further large haemorrhage, but do not close the opening in the artery; therefore, at each pulsation a little blood escapes and then goes back into the artery, communicating a rhythmic movement of expansion to the pocket of blood. This pulsating haematoma will be converted into an aneurysm by the progressive formation of a connective tissue membrane at its periphery. This membrane is insufficiently resistant to prevent a slow increase of the haematoma, and it will be necessary to operate.

When, in aneurysms resulting from bullet-wounds, the projectile has passed between an artery and a vein running parallel with it, injuring both the artery and the vein, it creates a communication between them through which part of the arterial blood passes directly into the vein and returns to the heart. There is only one treatment in such cases: surgical closure of this arteriovenous communication, which results in immediate cure.

Spontaneous arterial aneurysms appear on the large arteries of the trunk or the limbs and are due to a pathological decrease in the resistance of their walls. The resultant dilatation may be lateral (saccular aneurysm) or extended over a whole segment of the artery (fusiform aneurysm). The danger of an aneurysm is its tendency to slow enlargement to the point at which there is a risk of rupture, or else of embolism caused by a fragment of the clot which always forms on the inner wall of the pocket. Some aneurysms, however, may be well tolerated for many years. Operations for their removal have been performed successfully, thanks to Matas's technique (fig. 8), but only on aneurysms of the limbs or branches of the aorta. During recent years, in France and the United States, large aneurysms of the abdominal and thoracic aorta have been dealt with by restoring the circulation by means of a graft. This may include secondary branches of the large arteries which pass up to the skull and the upper limbs or down to the abdominal viscera and lower limbs (by-pass graft, fig. 9).

## *Surgery of the veins*

Operations on the veins are usually performed to remove the natural varices, that is to say, those that are not the result of phlebitis.

Attempts have been made to treat cases of phlebitis surgically, but removal of the initial venous thrombosis, which would seem a logical procedure, has not yet given the results hoped for, although some of the after-effects of phlebitis can be improved by localized resection of the varices or by excision of an ulcer followed by a skin graft.

Grafts have been made on veins, but their permeability is likely to be only temporary, although the operation may sometimes be sufficient to avoid serious consequences due to venous stasis. Progressive obliteration of the graft, in fact, often occurs, and this allows a collateral venous circulation to develop.

To obtain more lasting results it is necessary to use a new technique, the suspended suture (fig. 10). Without this device the sutured region gives way and ends by becoming obstructed because the venous pressure is low and does not permit resistance to scar contraction as effectively as arterial pressure does.

The pathology of veins is dominated by the abdundance of collateral circulation which is much better developed than when an artery is obliterated, and by the valvular insufficiency that spreads progressively in all the veins of an area affected by disease. But the valves play a very important part in the circulation of the blood returning to the heart. Their insufficiency is synonymous with stagnation in the veins, the results of which are oedema, ulcers, and nutritional disturbances in the skin.

Perhaps it will be possible one day to deal with these disorders by replacing almost the whole of a diseased vein with another vein that has valves. At present this cannot be done. When biologists will have found out how to enable a patient to tolerate a graft taken from another person, and to tolerate it for years, perhaps for ever, this technique will be capable of use to aid many patients. Meanwhile, prophylaxis is the best means of combating venous thromboses; after an operation is performed movement should be encouraged; the patient should get up soon after the operation and anticoagulants should be given; if a thrombosis is diagnosed, fibrinolytic drugs may be added, when these become available.

# Brain surgery

Gabriel MAZARS

*For a long time the brain was thought to be an inviolable and forbidden organ. The risk of damaging it surgically could only be taken in the light of exceptional anatomical and physiological knowledge of the innumerable mechanisms concealed inside it. In enormous advances made through the experimental work of the last thirty years or so, knowledge so precise has been accumulated that brain surgery is now one of the most clearly defined and best regulated branches of surgical technique. Daring attempts have recently been made to apply this technique to the treatment of psychological disorders.*

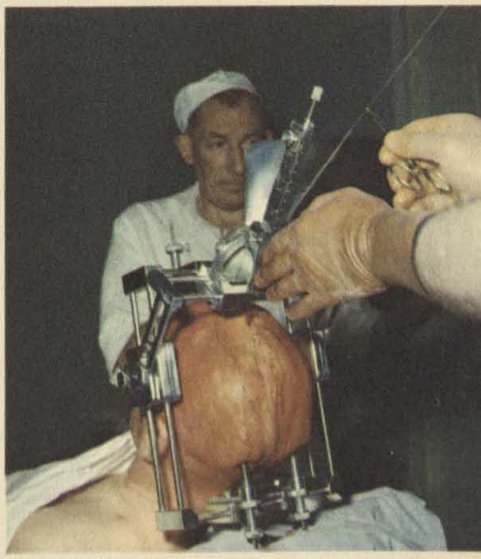


*Fig. 1. A stereotactic surgical operation: the 'frame' which is fixed onto the skull by four screws, enables the surgeon to direct an electrode with great precision, so that it reaches structures at the centre of the brain without injuring the regions traversed in order to reach them. (Photo by Professor Mazars).*

The brain and the cerebellum are enclosed in a highly resistant box formed by the skull and the meningeal membranes, which somewhat complicates the surgical approach to them. Surgeons have, however, known for a long time how to expose a part of the brain or cerebellum by cutting out a flap of bone or by trephining a more or less extensive opening. Today trephining is a well controlled operation which need not involve any risk.

Nevertheless, the brain is a fragile organ, sensitive to variations of temperature, pressure and humidity; it cannot be displaced or distorted, or taken out, as can the intestine or the kidney, and care must be taken to avoid variations of venous and arterial pressures or humoral changes that may bring about distension or collapse of the brain, or functional disturbances of the cells of which it is composed. This sensitivity to physical and chemical changes is quite unlike what one finds in other organs. The brain and the cerebellum constitute nothing but a mass of nerve cells and their axons; these cells are the most fragile in the whole body and an interruption of their oxygen supply for as little as three minutes, or a few minutes' arrest of the blood circulation, will cause their death. In order to nourish this mass of tissue, the metabolism of which is exceptionally intense and continuous, it is necessary to have a very rapid circulation and a good blood supply. The least obstruction of the venous return, the least injurious chemical influence, the least modification of the fluid environment, react on the functions of the cells; the damage to the brain that may result can produce a disturbance of consciousness, paralysis, or an epileptic crisis, to mention only the most usual phenomena.

The brain and the cerebellum, in fact, despite their relatively amorphous appearance, which seems homogeneous to the naked eye, represent a wonderful network of association pathways and groups of cells which control all man's conscious and unconscious activities. Incredibly compact and complex, united here in a few hundred grams are the controls of the mechanisms of speech, thought, perception of external sensations and their conscious representation, and of voluntary movements and their correct execution. Besides all these there is the control of the most diverse glandular functions, the regulation of temperature and blood pressure, heart and respiration

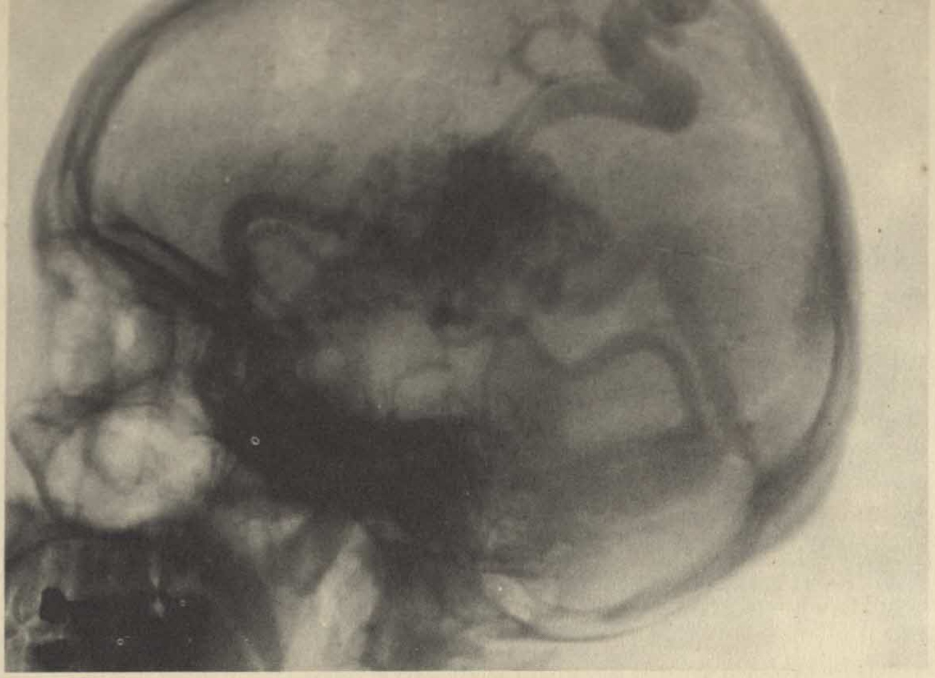


*Fig. 2. Radiograph of the veins and arteries of the brain of a patient suffering from an angioma (a benign tumour). The iodized substance which is injected into the carotid artery does not penetrate into most of the arteries and veins in the brain because the angioma absorbs most of the blood coming from the carotid artery. (Photo by Stirling).*

rhythms, and above all, consciousness, which remains the most astonishing function of this whole structure.

As it is impossible to start looking for a lesion or a particular anatomical system by digging into the brain tissue without doing more or less serious injury to certain nerve fibres or groups of cells, which may be of considerable importance, it is therefore essential in brain surgery strictly to locate the parts of the brain on which the operation is to be performed. When it is necessary to interrupt or destroy or reach a small part deep down in the brain, it is preferable to use special aimed procedures which make it possible to introduce needles, electrodes or small instruments through a minimal trephined opening with rigorous precision involving minimal damage to the areas traversed; this procedure is known as *stereotaxy*, and is among the current techniques of brain surgery.

In operating on the brain, haemostasis, or the stopping of bleeding, cannot be achieved by the usual procedures of general surgery: the cerebral vessels are extremely delicate and usually very small in diameter, so haemostat forceps cannot be used nor ligatures made with a thread; the brain tissue also is so fragile that it would not tolerate either plugging or compression, which are among the usual haemostatic methods. The large vessels are usually clamped by silver clips; in the smallest of them the blood is coagulated by high frequency electric currents. Application of absorbable tampons of porous substances impregnated with thrombin may be used to stop seeping from the finest vessels.

Anaesthesia for brain surgery also presents special problems. The fact that the brain can be handled, cut, coagulated, and stimulated electrically without pain makes it possible to carry out most of the stereotactic operations, as well as certain functional operations under a local anaesthetic. Actually, the only phase that could be painful during a neurosurgical operation is when the skin of the head is cut.

Most operations, however, are performed under a general anaesthetic, but although this helps to increase the patient's comfort, its chief importance lies in the fact that it makes it possible to influence the cerebral circulation and to control the brain's behaviour mechanically and pharmacologically, as well as to control its sensitivity to surgical attack.

Thus the anaesthetist, by creating a negative expiratory pressure, will be able to empty the cerebral veins and reduce the volume of the brain; at other times he will be able to lower the arterial pressure the moment a phase of the operation likely to result in haemorrhage begins; or by using hypothermia he will be able, harmlessly, to interrupt the cerebral circulation for several minutes.

## *Surgery of brain tumours*

Cerebral tumours have long been the main objective of brain surgery. Such tumours vary considerably: some are developed from and in the brain tissue, which they infiltrate; others, although they develop inside the skull at the expense of the meninges, the pituitary, or the blood vessels, penetrate the brain tissue, deforming it and pressing it back, but do not actually invade it. In each type of case the surgical problems are different.

Malignant tumours of the brain do not behave like malignant tumours elsewhere in the body. With very rare exceptions they do not form secondary tumours elsewhere, nor do they invade the lymph nodes, and recurrences of them are local.

A tumour in the skull soon creates an additional obstacle to the outflow of venous blood: the intracranial pressure rises. The veins in the retina, which are in direct communication with the cerebral veins, become abnormally distended, this being revealed by examination of the fundus of the eye which shows 'papillary stasis'.

In the diagnosis of cerebral tumours it is not sufficient to rely on neurological examination, simple radiography, and examination of the fundus of the eye; other investigations are essential.

The *electroencephalogram* studies modifications of the electrical activity of the brain's surface recorded simultaneously from a large number of points on the scalp. It is a means of functional investigation to locate areas of the brain that are disturbed. It cannot, however, indicate whether disturbance is caused by a tumour. Nevertheless, the localized data that it gives are very valuable and in a great many cases appearance of the tracings helps to confirm the diagnosis.

*Gammaencephalography* is based on the fact that certain substances marked with a radioactive isotope are fixed unequally on normal cerebral tissue and on that of cerebral tumours; after an intravenous injection of the radioactive substance, a chart is made of the fixation of the substance on the brain by means of a counter which records the individual particles emitted or measures the radiation. The anomalies recorded will show whether a tumour may be suspected.

*Ventriculography* consists of replacing the fluid in the ventricles of the brain with air or iodized oil; deformations of the ventricular system enable one to localize the tumours precisely.

*Arteriography* consists of injecting an opaque substance into the large arteries at the base of the neck; radiographs are taken rapidly and at short intervals. Tumours are often directly revealed by the wealth of abnormal vessels in their vicinity.

By these complementary methods, one can nowadays make a precise diagnosis. How soon this can be done depends on how the presence of the tumour is revealed, but the first symptoms of a cerebral tumour often give no cause for alarm.

Nowadays surgical removal is the basic treatment for a cerebral tumour. Neurosurgeons try to complete the treatment—especially if the tumour is malignant and is infiltrating the brain tissue—in order to lessen or retard the risk of a recurrence, by post-operative radiotherapy, the implantation of radioactive isotopes, or the action of physical or chemical agents on the periphery of the tumour, which are used for this with varying degrees of success.

## *Cerebral haemorrhages*

Next to cerebral tumours the lesion which most often makes surgical operation necessary is cerebral haemorrhage. Whatever the cause of this may be, the accumulation of blood subjects the brain tissue, enclosed in its rigid box, to severe compression. It is therefore necessary to perform emergency operations to remove blood clots and to stop the haemorrhage; otherwise, there is a risk of damage caused by the extravasation of blood, or an even graver risk of more serious effects due to compression, particularly of the brain stem. About 95 per cent of cerebral haemorrhages which are not operated upon result in death; emergency operations performed during the first few hours after the haemorrhage lower the mortality rate to less than 25 per cent.

## *Vascular malformations: aneurysms and angiomas*

Haemorrhages into the brain substance and the meninges, that is to say, those in which blood escapes into the meningeal spaces containing the cerebrospinal fluid, are mostly due to the rupture of a vascular malformation: this may be either an aneurysm, ie, a dilatation or lateral swelling in an artery, or an angioma, ie, a cluster of arteries and veins which are enormously dilated through being gorged with blood, like a sponge.

These malformations are often looked for, but are discovered only when haemorrhage occurs; as they endanger life, their immediate removal is essential.

Rupture of these malformations during an operation was for long a dramatic accident which added to the difficulties of dissection arising from the necessity to preserve normal blood vessels; nowadays the operative risks are minimal because complex anaesthetic methods can be used and also because

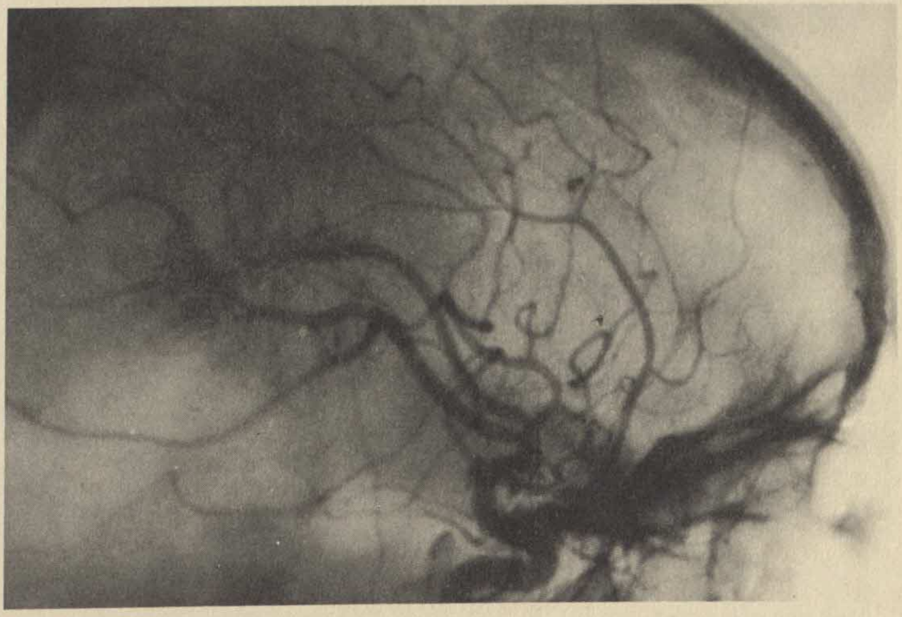


*Fig. 3. In this arteriogram of a patient suffering from a cerebral tumour, the iodized substance marks out the course of the normal cerebral arteries and injects the fine network of arteries and veins of the tumour. (Photo by Stirling).*

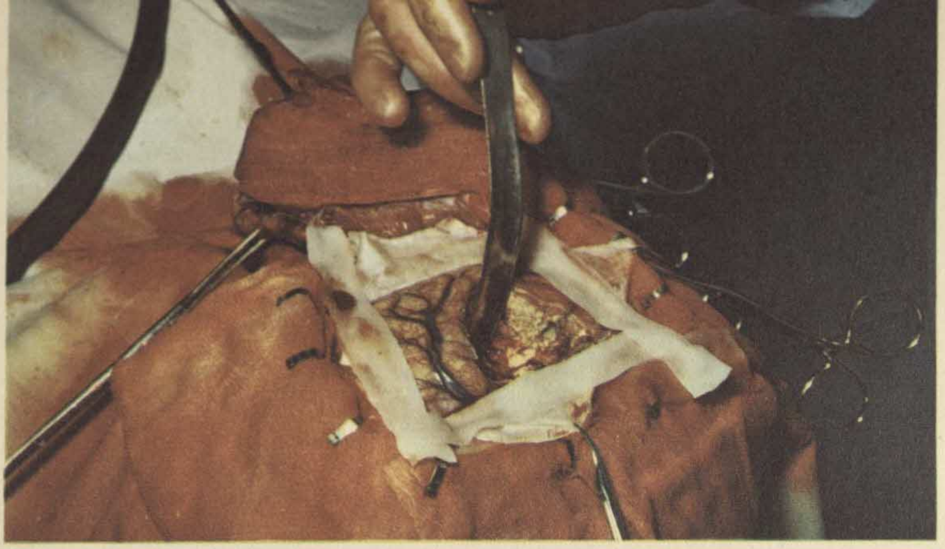


*Fig. 4. The brain is exposed by a 'flap' made by trephining; the separator held by the surgeon penetrates into a groove cut on the margin of a cerebral tumour. On the right is the normal brain with its cortical vessels; on the left, part of the tumour. (Photo by Professor Mazars).*

methods of localizing lesions are more precise, and operative tactics are better adapted to each case.

## *Functional surgery*

Besides radical surgery (tumours, cerebral haemorrhages, abscesses) and reparative surgery (vascular malformations, cranial injuries), *functional surgery* of the brain for dealing with pain, epilepsy, 'abnormal movements' and certain psychological troubles is becoming more and more important.

## *The surgery of pain*

The fibres which conduct sensations of pain are grouped in a slender bundle known as the spinothalamic tract, which ends in a voluminous group of cells in the centre of the brain called the ventral posterolateral nucleus of the thalamus. This spinothalamic tract can be cut just before its termination by means of an electrode directed by stereotaxy; this operation suppresses sensitivity to pain and heat in one half of the body, leaving intact other sensations and not affecting the motor tracts. Painful affections for which these operations are performed include pain due to cancer, injured nerves, certain arterial diseases, pain felt in the stumps of amputations, etc.

All pain is not associated with the arrival at the thalamus of painful stimuli carried by the fibres of the spinothalamic tract; to suppress these other kinds of pain or 'central pains', one tries nowadays to destroy that part of the thalamus in which the 'painful sensation' is elaborated, or to interrupt the pathways which allow the sensation to become a conscious one. These complex operations on the thalamus or on the pathways which connect it with the cerebral cortex are usually done by stereotaxy.

## *Epilepsy and abnormal movements*

If a 'scar' is left on the cerebral cortex or the nuclei in the grey matter of the brain by an infective process or by an injury, a localized asphyxia due to compression of the brain or an obliteration of blood vessels, this may be the starting point for an epileptic crisis; such scars are known as epileptogenic lesions. When they are so situated that they can be removed without disadvantage, it is advisable for this to be done.

Surgery for epilepsy deals especially with epileptogenic lesions of the cortex of the brain. Their localization can be discovered by means of an electroencephalogram. During the operation electrodes are applied directly to the suspected area in order to record an 'electrocorticogram', which makes it possible to mark out the points from which the greatest epileptic activity starts. This area is then removed, care being taken not to damage neighbouring areas, and a new electrocorticogram indicates whether the excision has been sufficient or whether it should be extended. The operation can be repeated as often as necessary until the epileptogenic area is entirely extirpated.

Most 'abnormal movements' or trembling, in particular those of Parkinson's disease, can be suppressed by creating a lesion a few millimetres in diameter, either in the pallium or in the thalamus; that is to say, in the nuclei of the grey matter in the centre of the brain. These operations are always done by stereotaxy and they constitute one of the most spectacular aspects of surgery; once the electrode is placed in position, the abnormal movements are suppressed in a few seconds, to the considerable astonishment of the patient.

## *Mental disturbances*

Under the general heading of 'psychosurgery' are grouped those operations which aim at modifying psychological behaviour and correcting certain forms of abnormal conduct. The oldest of these operations, frontal lobotomy, consists in dividing transversely the white matter of the frontal lobes in order to isolate the cortex of a part of the frontal lobe; nowdays operations better adapted to each particular case are preferred and surgeons use either the excision of certain convolutions (topectomies, cingulectomies), or destructions by stereotaxy of frontal-thalamic association tracts or destructions of thalamic nuclei.

# Plastic surgery

### *John M. CONVERSE*

*Plastic surgery is a speciality of surgery which deals with restoration or rearrangement of tissues of the body to correct disfigurement or disablement. Its origins are rooted in the need for alleviation of deformity of the face, a disability which sets aside the disfigured individual from his fellow men, for those who suffer from such a disability undergo countless indignities and social deprivations.*

Although plastic surgery is generally thought to be concerned with the face alone, it has expanded to include surgery of the superficial structures of the entire body.

The earliest written record of plastic surgery procedures is found in *Susruta,* the basic text of Hindu medicine which probably dates as far back as 600 B.C. One method describes repair of an ear lobe with a skin graft and another repair of a nose by means of a mobilized flap of skin from adjacent cheek tissue. In India, where amputation of the nose was a common form of punishment for crime, restoration of the nose was performed by the potters. In China the first recorded procedure was harelip repair during the Chin Dynasty (A.D. 221–317). Knowledge of these surgical procedures was probably transmitted from the East to the West by an interchange of knowledge between Greek, Jewish, Nestorian, Persian and Hindu scholars at the Persian School of Medicine at Gondi Sapor, a great centre of learning from the fifth to the tenth century, and through Arabic translations of eastern manuscripts.

In the Western World, Celsus, a Roman surgeon (25 B.C. to A.D. 50) was the first to describe restoration of tissue by mobilization and transplantation of neighbouring tissues. The Brancas, a father and son team, practised in Sicily in the late thirteenth and early fourteenth centuries. The elder Branca appeared to have knowledge of the Hindu method of nasal repair in his use of cheek tissue; Antonio, his son, went a step further in using the skin of the arm to build an entire new nose, immobilizing the arm until the skin had grown securely to the nasal area. Antonio also repaired lips and ears. The plastic procedures of the Brancas were practised in Italy by the Vianeo family in the fifteenth century.

Gaspare Tagliacozzi (1545–1599), of Bologna, wrote the first treatise on plastic surgery, published in Venice in 1597. During his time, deformity from venereal disease, mutilation in battle (many of Tagliacozzi's patients were warriors), and amputation of the nose as punishment for crime, all contributed to progress in the fine art of plastic surgery. After Tagliacozzi's death, plastic surgery fell into disrepute in the West, not to be revived again for two hundred years. The revival came from its original source, India.

The revival of the nasal restoration procedure (rhiniplasty) followed publication of a description of the procedure in the London *Gentleman's Magazine.* A correspondent in Bombay in a letter to the editor reported restoration of the nose of an Indian bullock-driver with the British Army in the war of 1792. He had been punished by having his nose amputated while a prisoner of the opposing forces. The technique, as performed by a member of the caste of the potters, was reported in full detail. Illustrations of the Hindu method were published by an English surgeon, J. C. Carpue, who gave an account of two operations he had successfully performed in 1816. In France, also, plastic surgery was being revived. In 1791 François Chopart excised the entire lower lip, part of the upper lip and part of the right cheek, restoring the area by mobilizing neck-skin into the defect.

Considerable progress was made during the nineteenth century, principally by French and German surgeons, and many of the techniques utilized today were established during this period. Trench warfare during the First World War resulted in innumerable severe wounds of the face. In France, the facially disfigured veterans formed an association, 'Les Gueules Cassées', a society for mutual aid. Much progress was made during and after the First World War under the instigation of Sir

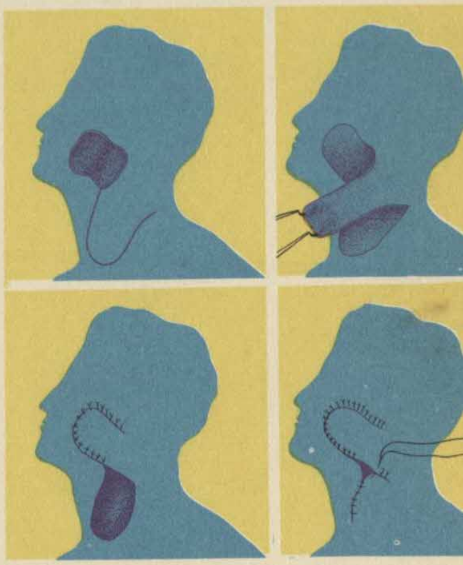


*Fig. 1. Correction of an imperfect cheek by means of a graft taken from the adjoining region. In order to cover the secondary wound, the skin of the neck is loosened and stitched directly.*

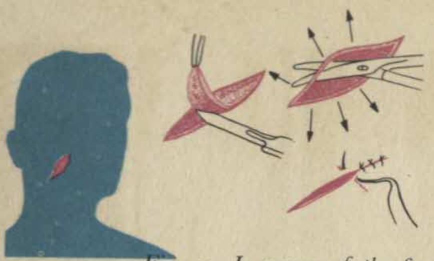


*Fig. 2. In surgery of the face, when the loss of tissue is great the superficial layer of the skin is separated from the basal layer, after which, thanks to the elastic properties of the epidermis, the wound is covered.*

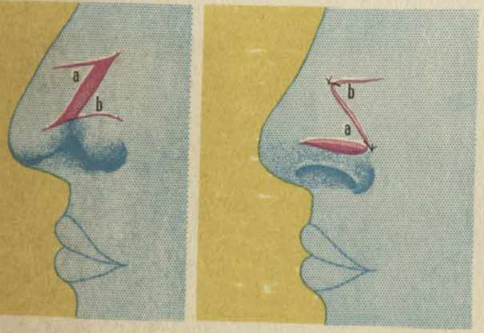


*Fig. 3. Correction of the* ala *of the nose by means of a Z-shaped graft.*

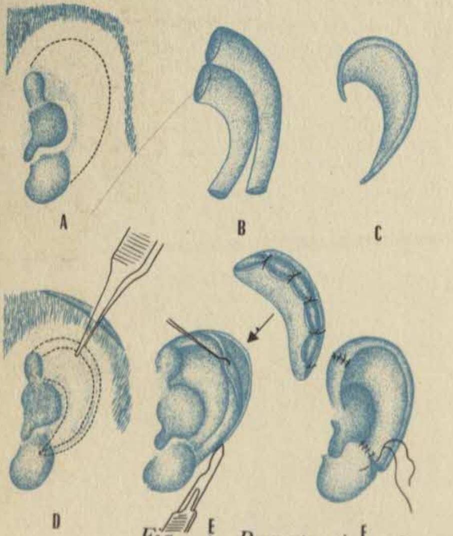


*Fig. 4. Reconstruction of an ear. A, the dotted line shows the position of the attachment of the auricle; B, pieces of cartilage taken from two ribs; C, the cartilage is shaped into an auricle; D, the cartilage is inserted under the skin; E, after healing, a mould is inserted to detach the auricle, and a fragment of skin is grafted under the ear; F, final retouches.*

Harold Gillies and T. P. Kilner in Great Britain, Morestin in France, Blair, Kazanjian and Ivy in the United States, and Filatov in Russia.

Between the World Wars, the invention of the dermatome in 1938 by Padgett, a plastic surgeon, and Hood, an engineer, provided surgeons with a new instrument for removing skin of a calibrated thickness for grafting. The dermatome proved invaluable in the Second World War, when a greater number of facial and body burns required widespread application of free-skin grafts. Whereas plastic surgery of the First World War was devoted primarily to maxillofacial, oral, and jaw repair, the advances between the wars, coupled with growing use of the tubed pedicle and the Padgett-Hood dermatome, broadened the scope of plastic surgery until, in the Second World War, the repair of any surface defect in depth ranged from 'the top of the head to the soles of the feet'.

Today minor miracles may be performed in the operating room. It is an interesting fact, however, that 2,000 years after *Susruta*, the Hindu procedure for restoration of the nose, with many refinements, remains one of the most outstanding and satisfactory plastic surgical procedures.

## *Principles of plastic surgery*

One of the simplest examples of plastic surgery is the excision of a scar and the closing of the wound margins. On the face this is done with the aid of high-power magnification and often barely a hairline scar is visible. When the wound is too large to be closed without tension, the adjacent skin may be undermined and freed from its underlying attachments (fig. 2). This mobilization and the natural elasticity of the skin may then permit closure. An area too large to be closed by direct suture requires either mobilization of a flap of adjacent skin, use of a free-skin graft or, in the case of very large defects, migration of tissue from another part of the body where skin is more abundant.

## *Skin flaps*

A skin flap is an area of skin and subcutaneous tissue that is entirely freed from its underlying and adjacent attachments except for a pedicle which remains attached to provide circulation. This pedicle is severed after the flap has healed into its new position. The secondary defect resulting from the removal of the flap may often be closed by direct suture, after undermining the adjacent tissues (fig. 1). When this procedure is not possible a free-skin graft from another part of the body is used. Flaps of skin adjacent to the primary defect are desirable, especially when operating on the face, because the skin of other parts of the body is different in colour and texture.

Many types of flaps may be used, depending on the type of defect and the position of available skin. One of the most useful is the Z-plast, which transposes two triangular flaps, changing the direction of skin tension. It is frequently used to lengthen contracted tissues along a scar line (fig. 3).

## *Tubed pedicle flaps*

Mobilizing skin from a part of the body distant from the wound is done by first making two parallel incisions, undermining the intervening skin and suturing the edges together into a tube. This leaves a raw area which may be closed by direct suture or with a free graft. When circulation has been established in the pedicle, one end is cut free and transplanted into the defect. If the pedicle has been made on the abdomen and is to be moved to the face, one end may be first transferred to the wrist, and when circulation has been established there, the abdominal end is detached and moved to the area of the defect (fig.5).

## *Free-skin grafts*

Skin grafts are unsuitable when the bed upon which they are placed is not sufficiently vascularized, such as a densely scarred or radiated area or denuded bone.

A free-skin graft is a relatively simple method of repairing a defect resulting from superficial tissue loss, as in burns, and is the best method of quick coverage of large open areas. The best dressing for an open wound is a skin graft.

When all of the fat is removed from the graft, by splitting the skin, a better union of base and graft occurs. Revascularization takes place from the base as well as the edges, and large surfaces can be covered. Concomitantly, the area from which the graft was taken retains its regenerative elements and a new layer of epithelium is generated.

Large split grafts are obtained by means of a special skin-graft knife or the dermatome, both instruments being adjusted so that the exact thickness desired may be removed.

Grafts from one person to another (homografts) will not survive permanently, but they are useful as a temporary dressing for burns when the patient has insufficient skin of his own available for autografts.

## Cartilage grafts

Cartilage is obtained from the anterior portions of the lower three ribs and also, in smaller pieces, from the ear and nasal septum. Cartilage grafts are employed to provide a framework in reconstruction of an ear or nose and also for restoration of contour in defects of the facial skeleton and skull.

## Facial grafts

Fascia lata is a strong tough fibrous sheet of tissue found covering the lateral thigh muscles. Narrow strips of this tissue are used as slings to support sagging tissues of a partially paralyzed face, such as an immobile eyelid, or corner of the mouth. It has also been used as a filler underneath the skin to restore contour, and for relining a damaged joint.

## Bone grafts

Bone grafts are employed extensively to re-establish continuity between separated fragments of bone and as contour-restoring material. Bone is carved to fit the defect or is used as strips or chips or may be ground up, as best serves the purpose. It has, however, four requirements essential for success: absence of infection; a well-vascularized, non-scarred bed; contact with adjacent bone, and complete immobilization during healing. Bone grafts are usually obtained from the hip bone (ilium) or the ribs.

## Nerve grafts

Occasionally a branch or a number of branches of this facial nerve must be sutured after having been severed accidentally. Paralysis of the facial muscles occurs when the continuity of this nerve has been broken. Suturing restores function, as does grafting when a section of the nerve has been destroyed, but in both instances recovery is a slow, gradual process.

## Composite grafts

Grafts of dermis and fat fill out depressions caused by deficiency in the subcutaneous tissues in the face. Skin and fat from the buttocks serve as filler to build up the contour of underdeveloped breasts. In such cases the top layer of skin containing the hair follicles must be removed; the rate of absorption of these tissues is considerable, however, and with fat grafts especially, cannot be predetermined.

Burns are high on the list of accidents. Early treatment by split-skin grafting has already been mentioned. Late reconstruction in these cases entails removal of scar contractures and replacement of flaps, tubed pedicles, or grafts.

Among the congenital deformities which call for plastic surgery are cleft lip (harelip), cleft palate, absence of an ear, oversized or undersized lower jaw, excision of birthmarks, and abnormalities of the genitals. Rebuilding of an ear demands the highest technical and artistic skill and still remains one of the unconquered frontiers of surgery, for the auricle is a complex structure. The cartilage framework must be carved from rib cartilage and this must be covered with living skin on both sides. Because viability must be considered at all times, several operations are necessary, allowing circulation to become established between stages (figs. 4 and 6).

While in former days syphilis was one of the most mutilating of diseases in the Western World, cancer now appears to be the greatest destroyer of living tissue. Cancer of the lips, eyelids and nostrils calls for excision of the diseased area and, when possible, immediate reconstruction (fig. 7). In some of the more malignant tumours. after radical excision of tissues, the area is first allowed to heal and a period of time to elapse before reconstruction lest the tumour recurs. Another condition treated by the plastic surgeon is bed sores in paralytic patients. Skin flaps are useful in these cases, where adequate circulation is essential.

A part of a plastic surgeon's practice is strictly cosmetic, often because of the widening of the world of entertainment, where a too large or too small nose, protruding ears or wrinkles may mean the difference between success and failure in a career. Old age, too, brings problems that certain people cannot face; they demand face-lifting and removal of sagging tissues around the eyes. In women, over-large or sagging breasts may also be corrected. In the end, however, the main objective of plastic surgery is best expressed in the words of Tagliacozzi:

'We bring back, re-fashion and restore to wholeness the features which nature gave but chance destroyed, not that they may charm the eye, but that they may be of advantage to the living soul, not as a mean artifice but as an alleviation of illness, not as becomes charlatans, but as becomes followers of the great Hippocrates. For although the original beauty of the face is indeed restored, yet this is only accidental, and the end for which the physician is working is that the features should fulfill their offices according to nature's decree.'

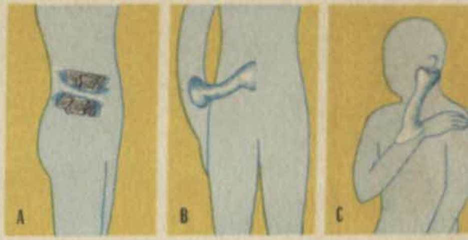


*Fig. 5. Transfer of skin from the hip to the cheek by tubular grafts.*

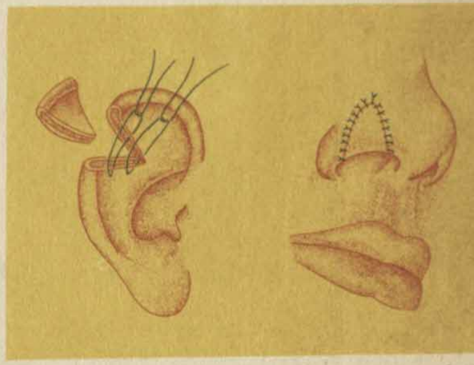


*Fig. 6. Mixed graft taken from the auricle of the ear to correct the* ala *of the nose after removal of cancerous tissue.*

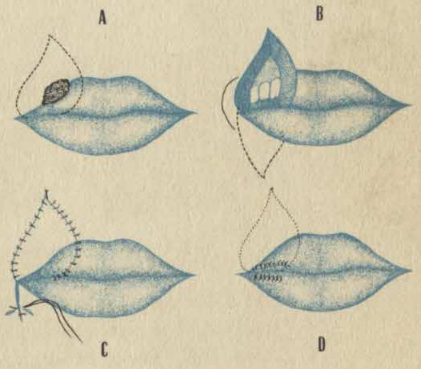
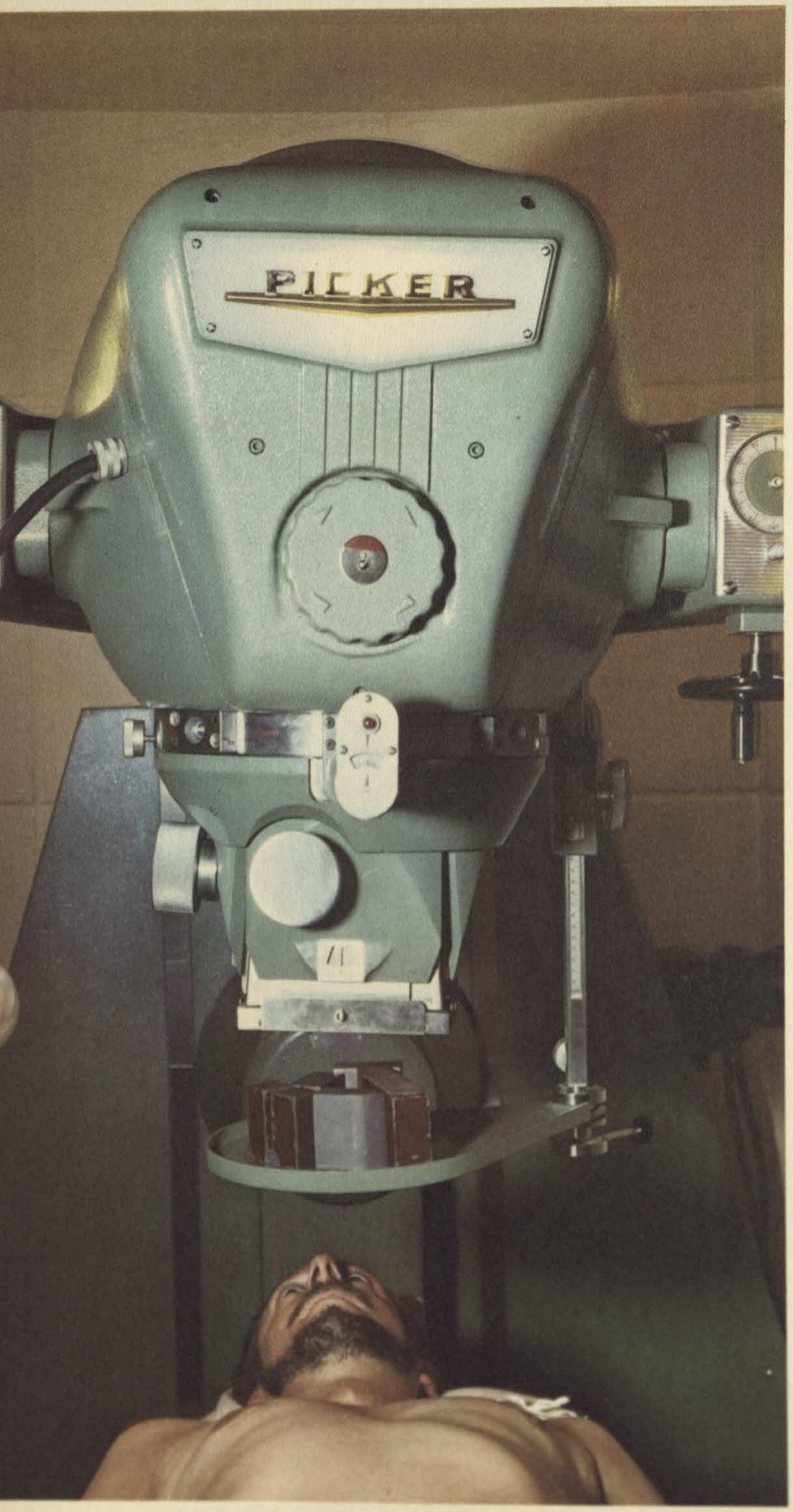
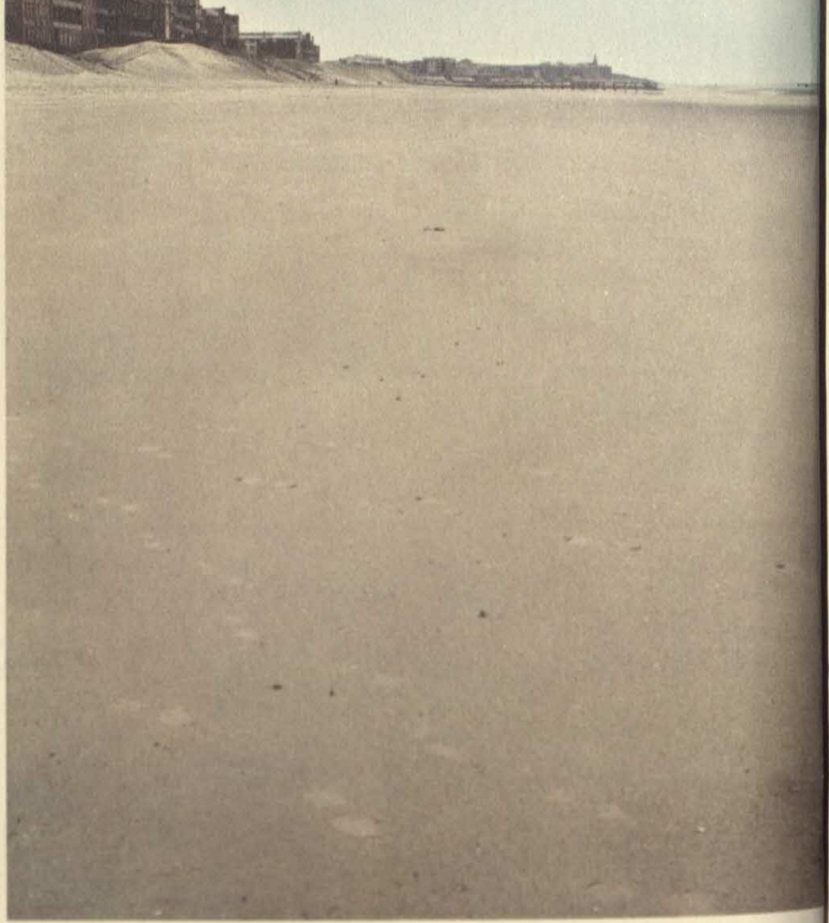


*Fig. 7. Remodelling of the lip after removal of a cancerous tumour, A. At the first stage (B, C,) a graft taken from the lower lip is applied to the upper lip. The commissure is then lengthened (D) by an incision followed by suture.*

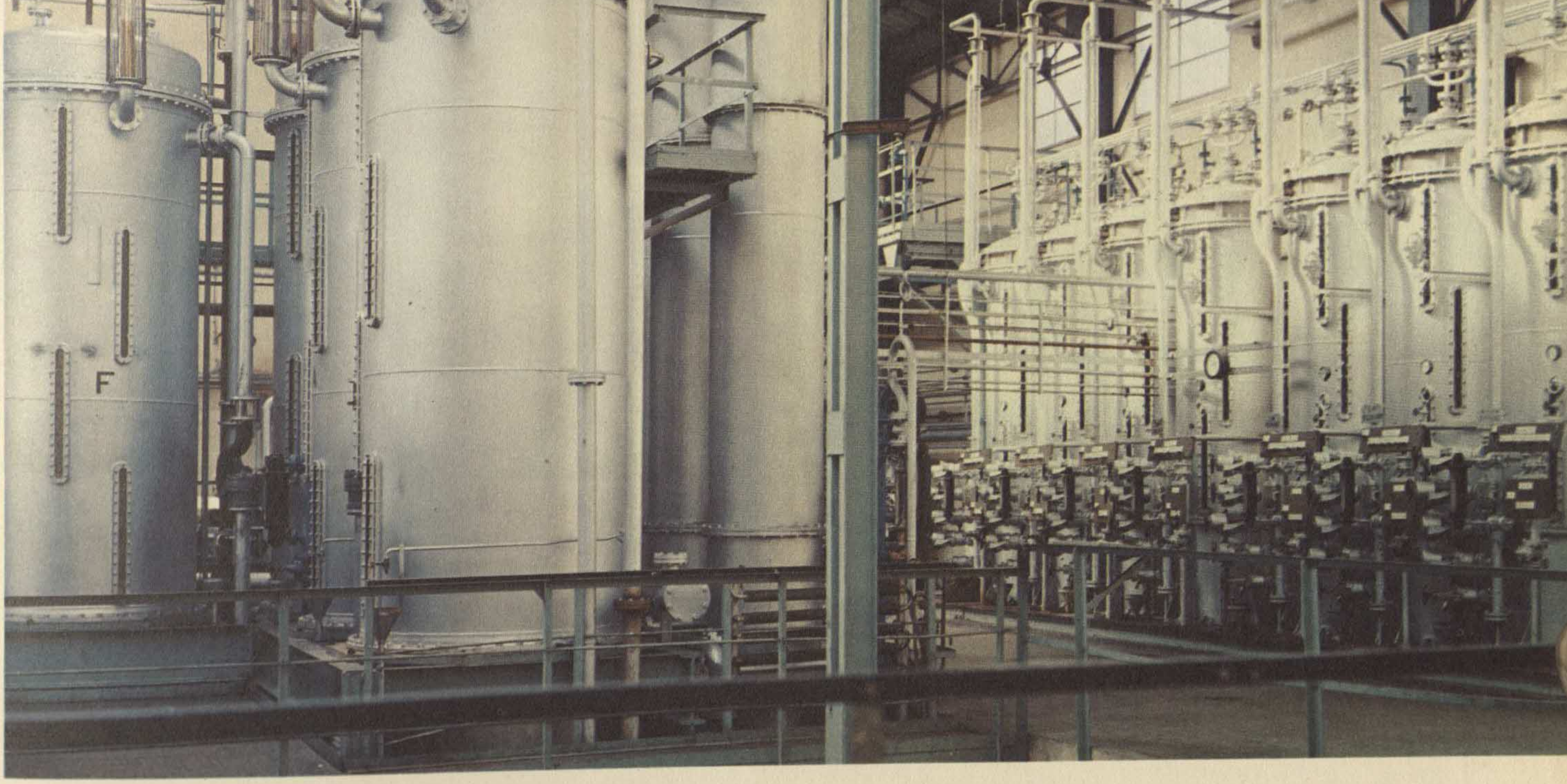


# PART FIVE



*Apart from its use of clinical, surgical and therapeutic methods, medicine aims at reconditioning the patient. Hence the importance not only of hospitals, but of clinics, convalescent homes, and sanatoria. Therapy will, of course (photograph on the left), remain indispensable,*

# *Care of the patient*



*nor is it likely that the imposing machinery of pharmaceutical laboratories (photograph on the right) will one day cease to function; but it is the restorative periods in health resorts or beside the sea (photograph in the centre) which constitute the last and most satisfying stage in the re-adjustment of the human body. (Photos Lod: on the left, at the Centre Curie, Paris; in the centre, at a well-known health resort; on the right, at the Société des Usines Chimiques,-Rhône-Poulenc, Usine d'Elbeuf).*

# Hydrotherapy

*Charles DEBRAY*

*Water-cures, already much in vogue in classical times, have kept all their uses. Thanks to a better understanding of the properties of medicinal waters and the progress of medicine in general, they have even become an indispensable adjunct to certain forms of medical treatment. The benefits of climatic treatment are nowadays also well known.*

Balneology includes all methods of treatment by medicinal waters. This term, incidentally, seems to be more appropriate than 'thermal' or 'mineral' waters because it includes certain cold springs and waters of low mineral content.

Balneology is one of the oldest therapeutic methods in existence. Even before the Roman conquest, thermal springs were used in the treatment of certain diseases. Invasions, European conflicts and civil wars often prevented access to the springs, but when peace returned, such treatment came back into favour.

With easier methods of travelling, introduced since the beginning of the last century, the development of thermal treatment has been speeded up, and during the last thirty or forty years objective tests of thermal cures have been made by scientific hydrotherapy. The teaching of both hydrotherapy and climatology is now included in the curricula of many European medical schools.

## Medicinal waters

The geological origin of medicinal waters varies. Many of them percolate through the soil, their mineral content being due to the nature of subterranean rocks. Others, which come from very deep levels through faults in volcanic rocks, are hot and radio-active, and have a mineral content that may be both low and complex; such springs consist in part of water not derived from rain, produced by the dehydration of rocks deep in the earth's crust, superheated and under pressure, or from the combustion of hydrogen.

The *action* of medicinal waters depends on various factors, all of which are perhaps not well understood; these include their chemical composition and physical characteristics, in particular their temperature, the presence of elements which, although possibly existing only in small amounts, are biologically very active, and the methods by which such waters are used, whether externally or for drinking, etc.

Their *chemical constitution* does, however, make possible a convenient, if somewhat rough and ready classification of their therapeutic virtues. The table on the opposite page and the map on the pages immediately following show the principal thermal resorts in France and other European countries, according to the composition of their waters and the medical indications for their use.

Some very hot waters with a low and complex mineral content (ie, containing few or many metallic salts), are rich in short-lived radio-active gases and have a sedative effect, which is tranquillizing and remarkably analgesic. For this reason they are used, especially in the form of baths, for certain diseases of the nervous system, the female genital system, the digestive system, the circulatory system (heart, arteries, and veins) and in numerous rheumatic afflictions.

*Cold* waters containing trace elements are strongly diuretic, and waters containing calcium sulphate are used to eliminate water and salts in the urine. These two groups of waters, which are used for drinking, are especially to be recommended in diseases of the kidney and the urinary system and in nutritional diseases.

Waters containing *magnesium*, and calcium and magnesium sulphates, are laxatives. Used as drinks, they regulate the passage of the contents of the bowel and are beneficial in diseases of the large intestine.

Waters containing *bicarbonates* are very numerous. Those which are warm and particularly rich in carbonic acid (*carbon dioxide gas waters*) are used as baths in diseases of the cardiovascular system (hypertension, arteritis, and coronary disease).

Waters containing *sodium bicarbonate* (eg, Vichy water) and those containing sodium and *calcium bicarbonates*, when taken as drinks have a remarkable action on the liver, the bile and pancreatic ducts, and the stomach. They are much used for chronic diseases of these organs.

*Warm and cold sulphurous* waters, containing sodium or calcium, are used specifically for diseases of the ear, nose, and throat, either by inhalation, by snuffing them up, or as gargles or nasal douches. Some of these warm sulphurous waters have a remarkable antirheumatic action, used either as ordinary baths or as vapour baths.

Waters that are rich in salt (*strong sodium chloride* waters) have a distinct effect on lymphatic diseases, diseases of the bones, and gynaecological infections.

Some chemical elements give certain waters particular virtues: *arsenic*, taken orally in small doses, has a tonic effect on children and, used as an aerosol or for inhalation, it acts on respiratory infections; *iron*, when it is ingested, gives water an anti-anaemic action; *copper*, by its local action, cures some chronic skin diseases.

Waters which do not contain a dominant chemical may nevertheless have therapeutic effects: thus some tepid waters, called *weak sodium chloride* waters, are used externally for spontaneous or post-traumatic osteoarthritic affections; certain other waters, called *indeterminate* waters, which contain sulphur and arsenic, are very active when used for nebulization or as aerosols in the treatment of asthma and affections of the upper respiratory tract.

## *Methods of using medicinal waters*

Methods of administering medicinal waters are very varied: they may be taken as *drinks*, for the treatment of nutritional diseases, or diseases of the kidneys or the digestive system and its associated organs: applied

## PRINCIPAL FRENCH WATERING PLACES

with their indications

| watering places | circulatory system, digestive system, liver. | bile duct | kidneys, urinary system, nutritive disorders | skin affections | gynaecology | lymphatic disorders and anaemia | bones, joints, rheumatism, after-effects of wounds | nervous system | respiratory tract, ear, nose, and throat | dominant chemical qualities |
|---|---|---|---|---|---|---|---|---|---|---|
| Abatilles-Arcachon (Gironde) | | | ● | | | | | | | cold, poor in metallic salts |
| Aix-les-Bains (Savoie) | | | | | | | ● | ● | | sulphurous |
| Aix-en-Provence (B.-du-R.) | ● | | | | | | | | | very hot, poor in metallic salts |
| Allevard (Isère) | | | | | | | | | ● | sulphurous, cold |
| Amélie-les-Bains (Pyr. Orient.) | | | | | | | ● | | ● | sulphurous, hot |
| Ax-les-Thermes (Ariège) | | | | | | | ● | | ● | sulphurous, hot |
| Bagnères-de-Bigorre (Htes-Pyr.) | | | | | | ● | ● | | | very hot, poor in metallic salts |
| Bagnoles-de-l'Orne (Orne) | ● | | | | | | | | | cold, poor in metallic salts |
| Bains-les-Bains (Vosges) | ● | | | | | | | | | very hot, poor in metallic salts |
| Barèges (Htes-Pyr.) | | | | | | | ● | | | sulphurous |
| Biarritz (B.-Pyr.) | | | | | ● | | ● | | | rich in chlorides and sodium salts |
| Boulou (Le) (Pyr. Orient.) | | ● | ● | | | | | | | bicarbonates and sodium salts |
| Bourbon-Lancy (Saône-et-Loire) | ● | | | | | | ● | ● | | very hot, weak chlorides |
| Bourbon-l'Archambault (Allier) | | | | | | | ● | ● | | hot, weak chlorides |
| Bourbonne (Hte-Marne) | | | | | | | ● | ● | | very hot, weak chlorides |
| Bourboule (La) (Puy-de-Dome) | | | | ● | | ● | | | ● | arsenic |
| Brides-Salins-Moutiers (Savoie) | | ● | ● | | | ● | | | | sulphurous, sodium and magnesium salts, chlorides |
| Bussang (Vosges) | | | | | | ● | | | | iron salts |
| Capvern-les-Bains (Htes-Pyr.) | | ● | ● | | | | | | | cold, sulphurous, calcium and magnesium salts |
| Cauterets (Htes-Pyr.) | | | | ● | | | ● | | | hot, sulphurous |
| Challes-les-Eaux (Savoie) | | | | | | | | | ● | sulphurous |
| Chatel-Guyon (Puy-de-Dome) | | ● | | | | | | | ● | bicarbonates, chlorides and magnesium salts |
| Chaudes-Aigues (Cantal) | | | | | | | ● | | | very hot, poor and rich in metallic salts |
| Contrexeville (Vosges) | | ● | ● | | | | | | | cold, sulphurous, calcium and magnesium salts |
| Dax (Landes) | | | | | ● | ● | ● | | | sulphurous, radioactive muds |
| Divonne-les-Bains (Ain) | | | | | | | | ● | | cold, poor in metallic salts |
| Enghien (Seine-et-Oise) | | | | ● | | | ● | | ● | cold, sulphurous |
| Evian (Hte-Savoie) | | ● | ● | | | | | | | cold, poor in metallic salts and magnesium salts |
| Forges-les-Eaux (Seine-Marit.) | | | | | | ● | | | | iron salts |
| La Léchère (Savoie) | ● | | | | ● | | | | | very hot, sulphurous |
| Lamalou (Hérault) | | | | | | | ● | ● | | very hot, poor in metallic salts |
| Luchon (Hte-Garonne) | | | | | | | ● | | ● | hot, sulphurous |
| Luxeuil (Hte-Saône) | ● | | | | ● | | | | | very hot, chlorides |
| Miers-Alvignac (Lot) | | ● | | | | | | | | strong sulphurous, sodium and magnesium salts |
| Moltig (Pyr. Orient.) | | | | ● | | | | | ● | hot, sulphurous |
| Mont-Dore (Puy-de-Dome) | | | | | | | | | ● | indeterminate |
| Néris (Allier) | | | | | ● | | ● | ● | | very hot, poor in metallic salts |
| Plombières (Vosges) | | ● | | | ● | | ● | | | very hot, poor and rich in metallic salts |
| Pougues-les-Eaux (Nièvre) | | ● | ● | | | | | | | bicarbonates, sodium and calcium salts |
| Preste (La) (Pyr. Orient.) | | | ● | | | | | | | sulphurous |
| Roche-Posay, La (Vienne) | | | | ● | | | | | | bicarbonates, calcium and silicon salts |
| Royat (Puy-de-Dome) | ● | | | | | | | | | carbon dioxide gas |
| Saint-Amand (Nord) | | | | | | | ● | ● | | sulphurous, radioactive muds |
| Sainte-Aré-Decize (Nièvre) | | ● | | | | | | | | strong sulphurous, sodium and magnesium salts |
| Saint-Christau (B.-Pyr.) | | | | ● | | | | | | copper salts |
| Saint-Gervais (Hte-Savoie) | | | | ● | | | | | ● | sulphurous |
| Saint-Honoré-les-Bains (Nièvre) | | | | | | | | | ● | sulphurous and arsenic salts |
| Saint-Nectaire (Puy-de-Dome) | | | ● | | | | | | | bicarbonates |
| Saint-Sauveur (Htes-Pyr.) | | | | | ● | | | | | sulphurous |
| Salies-de-Béarn (B.-Pyr.) | | | | | ● | ● | ● | | | strong chlorides and sodium salts |
| Salins-les-Bains (Jura) | | | | | | ● | ● | | | chlorides and sodium salts |
| Thonon (Hte-Savoie) | | ● | ● | | | | | | | metallic salts |
| Uriage (Isère) | | | | ● | ● | | ● | | | hot, sulphurous |
| Vals-les-Bains (Ardèche) | | ● | ● | | | | | | | bicarbonates, sodium salts |
| Vichy (Allier) | | ● | ● | | | | | | | bicarbonates, sodium salts |
| Vittel (Vosges) | | ● | ● | | | | | | | cold, sulphurous, calcium and magnesium salts |

*externally* they may be used for neurological and rheumatic diseases and diseases of the ear, nose and throat; or they may be used by *direct application* to mucous membranes for diseases of the colon and for gynaecological and nose and throat disorders; *inhalation* of aerosols and mists is the method used for affections of the respiratory tract.

At most thermal resorts the drinking of waters and their external use are both practised, though usually one method is used more than the other. Treatment is nowadays almost always associated with physiotherapy and techniques to ensure functional re-adaptation; and sometimes 'relaxation treatment' is given, which is so useful in cases of nervous fatigue, from which the majority of patients suffer.

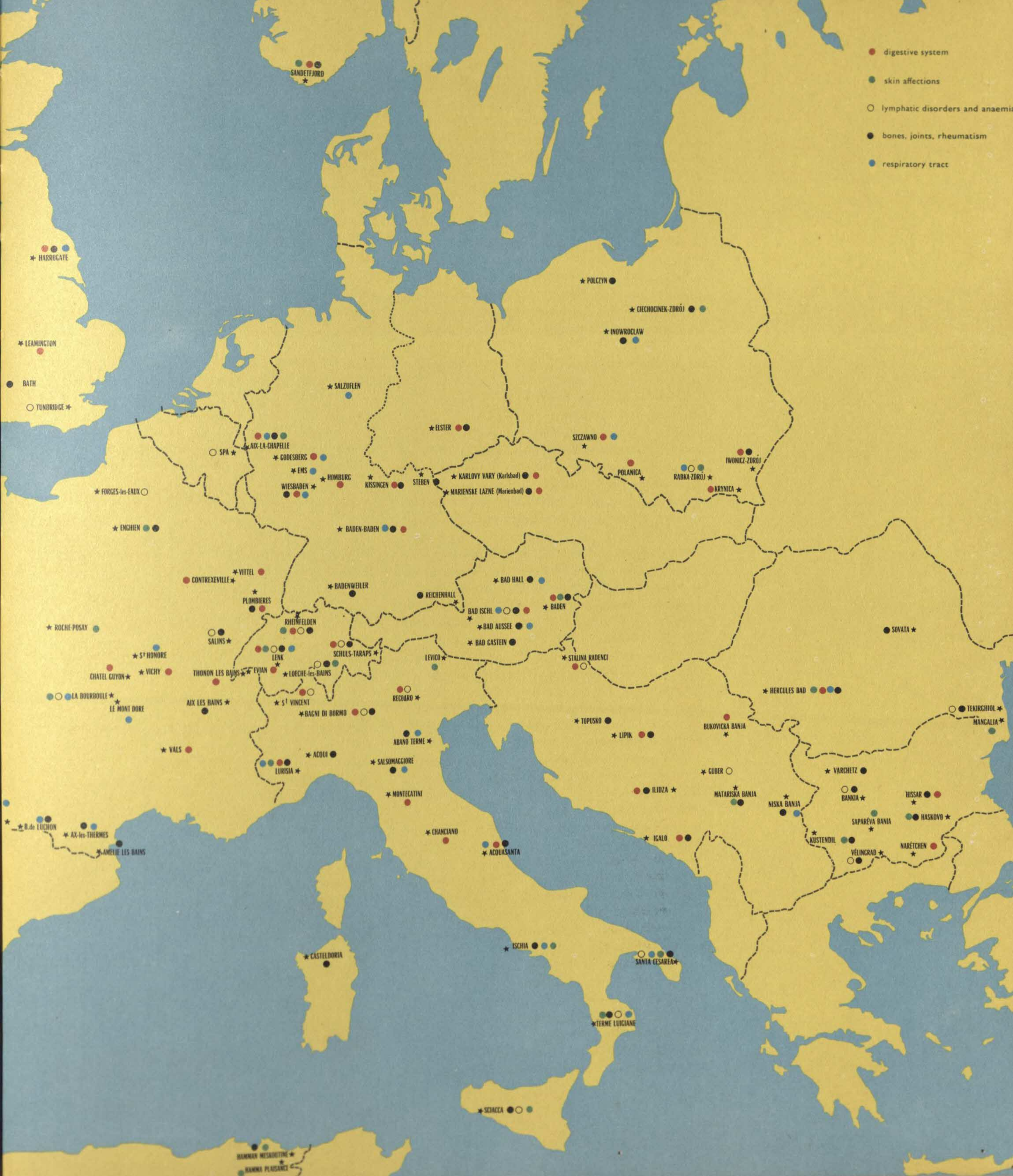
## *Opportunities and results*

Therapy involving the use of medicinal waters is a complex process which must be strictly controlled by a thermal specialist.

Only *chronic diseases* are amenable to balneology; it is of no use for acute conditions. Treatment usually lasts about three weeks, though there may be exceptions, depending on the disease and the nature of the resort. As a rule, treatment is given between May and September, though for commercial reasons the thermal season is extended for as long as possible. Some resorts which have a mild climate even provide treatment in winter.

In contrast with resorts in the United States, where many of them are merely 'health towns', European resorts have achieved a reputation for precise *specialization*: patients suffering from well-defined diseases are treated at resorts chosen by specialists in accordance with the nature of the disease.

The immense advances in surgery and in the use of anticoagulant drugs, antibiotics, and hormones, mean that diseases which formerly could have been treated only by balneology can now be cured more easily and more quickly, but this does not mean that balneology has ceased to develop. It takes over where antibiotics and hormone therapy stop. Often it completes post-operative treatment. This is because it alone, or almost alone, deals with the 'background', which it acts upon favourably. It is also due to the arrival of a new category of clients, the elderly whose lives have been prolonged by medicine; treatment of those injured in road or industrial accidents, more numerous than previously; and treatment of allergies or of patients suffering from toxic effects or merely from fatigue, whose numbers increase with the


digestive system
skin affections
lymphatic disorders and anaemi
bones, joints, rheumatism
respiratory tract
SANDETFJORD
HARROGATE
LEAMINGTON
BATH
TUNBRIDGE
POLCZYN
CIECHOCINEK-ZDRÓJ
INOWROCLAW
SALZUFLEN
ELSTER
SZCZAWNO
SPA
AIX-LA-CHAPELLE
GODESBERG
EMS
HOMBURG
WIESBADEN
KISSINGEN
STEBEN
KARLOVY VARY (Karlsbad)
MARIENSKE LAZNE (Marienbad)
POLANICA
RABKA-ZDRÓJ
IWONICZ-ZDRÓJ
KRYNICA
FORGES-les-EAUX
ENGHIEN
BADEN-BADEN
VITTEL
CONTREXEVILLE
PLOMBIERES
BADENWEILER
REICHENHALL
BAD HALL
BADEN
BAD ISCHL
BAD AUSSEE
BAD GASTEIN
RHEINFELDEN
ROCHE-POSAY
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LENK
SCHULS-TARAPS
CHATEL GUYON
VICHY
THONON LES BAINS
EVIAN
LOECHE-les-BAINS
LEVICO
STALINA RADENCI
LA BOURBOULE
LE MONT DORE
AIX LES BAINS
S^T VINCENT
RECOARO
BAGNI DI BORMO
HERCULES BAD
TEKIRGHIOL
MANGALIA
TOPUSKO
LIPIK
BUKOVICKA BANJA
ABANO TERME
VALS
ACQUI
SALSOMAGGIORE
LURISIA
GUBER
VARCHETZ
ILIDZA
MATARISKA BANJA
NISKA BANJA
BANKJA
HISSAR
MONTECATINI
SAPARÉVA BANIA
HASKOVO
B. de LUCHON
AX-les-THERMES
AMELIE LES BAINS
CHANCIANO
IGALO
KUSTENDIL
ACQUASANTA
VELINGRAD
NARÉTCHEN
ISCHIA
CASTELDORIA
SANTA CESAREA
TERME LUIGIANE
SCIACCA
HAMMAN MESKOUTINE
HAMMA PLAISANCE

strain of modern life. The scope of balneology has been enlarged by the advent of social medicine, which has enabled impecunious patients to have thermal treatment which would otherwise have been beyond their means.

The development of *child* balneology is no less important. Children are highly sensitive to thermal treatment and it is perhaps with them that the best and most lasting results are obtained.

Recently, an important advance has been made, in that it has become possible to analyse the results of thermal treatment far more precisely than has happened hitherto. This is due to two factors: the progress that has been made in techniques of medical investigation, and the publication of statistics issued by watering places as a result of social health services. The medical profession has thereby been left in no doubt about the satisfaction of patients who have undergone thermal treatment. The functional tests of respiration in asthmatics, radiographs and endoscopies of sufferers from digestive troubles, and biological tests of hepatic and rheumatic cases, have provided objective evidence that this is not merely a phenomenon of 'thermal faith'.

Interpretation of the results of balneology is also helped substantially by numerous reports of experiments carried out on animals at the outlets of thermal springs and in medical laboratories.

The full results could not be better expressed than by recent statistics of various French centres. Their value is guaranteed by the uniformity of the therapeutic data and by systematic examinations made after treatment. At Lyons in 1954, 40 per cent of results were very good or good; 44 per cent were temporary or partial in cases of chronic rheumatism. These figures establish the value of balneology beyond dispute.

## Climatic resorts

The therapeutic uses of climate are less precise than are those of other branches of curative medicine. The favourable effects of certain climates have long been known, and although doctors still cannot give a coherent explanation of them, they are of great interest to them. Western Europe is blessed with a wealth and diversity of therapeutically active climates, and medicine uses their possibilities to the full. This brief chapter deals only with basic ideas.

Each climate is characterized by a large number of factors: its *telluric* features (geographical situation, nature of the soil); its *atmospheric* features (temperature, atmospheric pressure, carbon dioxide, ozone, water vapour, fogs, bacteria, the electrical state of the air, and wind conditions); and its *actinic* characters (intensity of solar radiation, proportion of ultra-violet rays).

Some of these factors, such as cold, wind, dry air, light-intensity, have a *stimulant* effect; others are *sedative*—constant temperature, warmth, humidity, absence of wind.

The simplest and commonest form of climatotherapy is *heliotherapy*: exposure of the naked body to the sun, with the head and especially the eyes shaded. Heliotherapy must be very carefully supervised in order to avoid sunstroke, conjunctivitis, insolation (effect of heat), and especially the reawakening of an unrecognized pulmonary tuberculosis. Heliotherapy is salutary, however, in cases of non-pulmonary tuberculosis, and of rickets, lymphatic disease, and some local and general affections.

*High altitude* climates, characterized by cold, pure, windy air, low atmospheric pressure, and intense ultra-violet radiation have marked physiological effects, such as an increase in the number of red blood cells and the stimulation of the heart and the vascular and respiratory systems. These effects are dangerous for old people or for anyone suffering from cardiac or respiratory insufficiencies, but are excellent for asthmatics, tuberculous patients who have no fever, anaemic patients, those suffering from malaria, and for convalescents in general.

The climates of certain *low altitudes* are extraordinarily sedative to urban neuropathic patients, or to those suffering from coronary disease or who have a bad cough.

A *marine* climate, with its stable temperature, humid winds and light-intensity, is tonic and stimulating. Sea-bathing completes this effect, provided that its duration and frequency are rationally controlled. It is especially good for rickety or debilitated children and for patients with non-pulmonary tuberculosis, but is bad for very old people or for anyone with heart or kidney disease, rheumatism, or pulmonary tuberculosis.

The injurious effects of *urban climates* are well-known, and individual and collective measures are necessary to prevent them: these include open-air schools, playing fields, air-conditioning of hospitals, and the abatement of smoke and fumes—problems which all require the collaboration of town dwellers, doctors and public authorities.

# The development of pharmacology

*René HAZARD*

*The rapid development of pharmacology has made it one of the most progressive branches of medicine. Devoted to the study of poisonous and therapeutic substances, and to the experimental analysis of their activity in the body, pharmacology is the basis of rational treatment. After making preliminary laboratory tests, the doctor then carries out clinical trials which, if they are satisfactory, allow the new substances to be made available to the public. This chapter explains the methods of pharmacology and how it draws up its balance sheet of successes and failures.*

Disease is bound up with the life of man, who is instinctively afraid of it because he fears suffering and, whatever stoics may say, fears death even more. Hence the instinctive search for means of alleviating pain and ensuring the cure of disease. In the beginning, man had at his disposal only the resources offered by nature, some vegetable, some animal, and some mineral. The simples, derived from plants, were the remedies most easily available and many medicinal plants still render valuable service, for example, opium and digitalis. Indeed, plants seem to offer apparently inexhaustible sources of drugs: for instance, recent applications of the properties of Rauwolfia and the immense number of discoveries made in the field of natural antibiotics opened up by the discovery of penicillin, and extracts of bacterial cultures, yeasts and fungi. The use of certain animal humours and organs was also instinctive long before the adoption of rational forms of pharmocological treatment which now provide such essential drugs as insulin. There are also mineral sources, such as bismuth and phosphorus.

The discovery of the active principles of natural products was a decisive step in research on drugs; thus quinine, isolated by Pelletier and Caventou, replaced cinchona, and morphine replaced opium. But progress in this branch of research did not consist only in applying pure and constant active principles to therapeutics. It also meant discovering the composition of these principles, their chemical formulae, and their physiologically active groupings. Knowledge of immense importance was gained which related the physiological or therapeutic activity of the products to their chemo-physical constitution. This relationship provides important indications on the modifications which it seems desirable to bring about in a molecule of known constitution in order to make it less toxic or more effective.

## *Isolation and synthesis of active pharmacological principles*

Recently, products derived from reserpine (one of the alkaloids of Rauwolfia) have been isolated, in which either a central neuroleptic action or a hypotensive action are predominant; indeed, it has been considered preferable to keep these actions separate, although the initial substance combined the two.

All synthesis of medicinal products is guided by this knowledge of the relation between the constitution of a product and its action, with a view to producing new products which have a given action. This 'directed' synthesis is, however, full of surprises and deceptions for the research worker. It would be wrong to think that because the market is full of new products, their manufacture is a simple matter. We shall see, in the course of this chapter, the obstacles with which the road is strewn. There are numerous drugs which

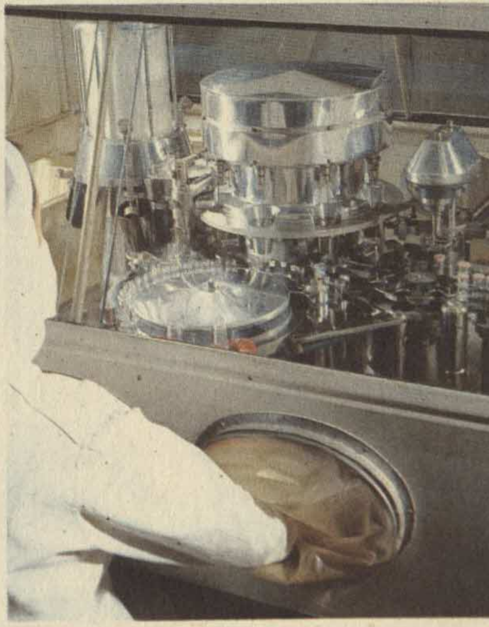

*Fig. 1. Rigorous aseptic conditions are necessary for the preparation of antibiotics for injection into the body. Here a machine is being used for the sterile separation of antibiotics. (Photo by the Societé Parisienne d'Expansion Chimique).*

produce appreciably similar results, although their molecular structure and even the chemical series to which they belong are entirely different. Isomerism also plays a part and isomers are known (with or without the power of rotation of polarized light) which differ from each other in their quantitative and even in their various qualitative effects to such an extent that in some cases their physiological actions are opposite.

It is sometimes found that a drug which was first used because of one particular and striking property may also come to be used successfully but unexpectedly for another. Some antihistamines, for instance, are no longer used only as such, but also as hypnotics. Procaine, although still used as a local anaesthetic, is also used as an inhibitor of the ganglia of the autonomic nervous system. Recently, it has been found that a product which was at first regarded as specific for the treatment of mycoses is also useful for the treatment of Parkinson's disease.

## *Trials of therapeutic substances*

All new drugs are first submitted to physical and chemical examination, for it is necessary to check the identity, the purity and the constants (melting point, solubility, etc), of every drug, these being the guarantee that its manufacture is reliable and that its properties will remain constant. Chemists know the difficulties that lie between the pilot preparation of a drug and its industrial manufacture. The stability of the product must be checked before it can be sent to the laboratory for pharmacological tests.

The part played by these laboratories is nowadays very important. They must have on hand innumerable animals of various species, for the differences between the reactions of one species and those of another are sometimes surprising; herbivores, for instance, tolerate quantities of atropine which would kill man; rats, on the other hand, are especially sensitive to squill.[1]

It is therefore very important to determine the relative toxicity of a drug to several animal species, omnivores, carnivores, and herbivores. It is necessary to discover whether the toxicity is acute, when it shows itself after a single strong dose, or whether it is chronic when, after several repeated doses, it causes the experimental animals to show digestive, nervous or muscular troubles, effects on the blood, etc, which may be severe enough to cause death, even a long time after the drug has been taken. Certain organic derivatives of arsenic and antimony may prove to be fatal after a considerable lapse of time; they may seem to be well tolerated for a week or two, but when they have caused irreversible lesions in the body, toxic and possibly even fatal effects will suddenly appear. Even more delayed and hidden for a longer time, are the effects on the blood caused by numerous drugs which are generally considered to be harmless.

After this preliminary investigation of toxicity, examination begins of the different actions of the product on experimental animals. First, the principal actions on the main organ systems, central and autonomic nervous systems, heart and vascular system, digestive and neuromuscular systems, etc, are studied. It is of the utmost importance to investigate the mechanism of the drug's principal action and methods of reinforcing this, or, as the case may be, how to combat it, for pharmacology and toxicology are often interlinked. Knowledge of pharmacology is essential for the diagnosis and treatment of poisoning, whether accidental or otherwise, because cases of poisoning have increased dangerously since medicinal and other products, which have the most varied effects, have come into general use. These include insecticides, for example, and numerous products used for destroying pests.

Considerable work, then, still remains to be done because it is always necessary to determine as far as possible the secondary effects of every new product. It is very desirable to know them because some add to the usefulness of the product and others may be found to be useless or dangerous, in which case everything must be done to correct them. It is also necessary to determine the fate of a drug once it is in the body, its localization, the changes it may undergo, and the ways in which it is eliminated, in relation to the duration of its action.

All this kind of information, experimentally obtained, constitutes a record that the pharmacologist will in due course pass on to the physician. The latter will apply these data of toxicity and activity to treatment of the human subject with great caution. The pharmacologist will also let the physician know the methods of administering the drug and the routes by which it should be given, which appear to him to be most efficacious in the treatment of man.[2] In spite of all the precautions that must be taken before trying out a new drug on a human patient, clinical

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(1) Squill *is a bulbous plant belonging to the Liliaceas family, one species of which is used as a diuretic.*

(2) *Up to now, mention has been made only of experiments performed on normal healthy animals. But experiments are also made on animals subjected to disturbances of their normal functions which may recall the symptoms of certain diseases. When this stage has been reached, methods are sought for restoring the animal to a normal state by treating it with drugs, but cases where this is possible are rare. For example, to test the action of certain heart tonics, such as the derivatives of camphor, one first induces cardiac depression in the animal with a solution of potassium chloride. In the same way, the causing of epileptic crises in animals has given us new knowledge about anti-epileptic drugs. Notable progress has been made in the field of neuroleptic and tranquillizing drugs as a result of certain substances being discovered which, when given to animals, cause a modification of their behaviour which recalls certain nervous or psychological troubles observed in man.*

(3) *A moral problem of considerable importance arises here. Has the doctor a right conscientiously to withhold from a patient a proven remedy in order to ascertain the effect of a new drug—an effect that may not be fully understood? It may be hoped that in order to avoid criticism, the doctor would give such a drug only to patients who have volunteered to accept it on a trial basis.*

application remains the most important test of all, because only the clinician can judge its preventive and curative value. This stage is also the most delicate.[3]

It is necessary, of course, to take into account the gravity of the disease and the resistance and susceptibility of the patient. It has been said—and with good reason—that there are patients, but not diseases. What has now become a classical experiment, the *blank* or *control test*, shows that in a significant proportion of cases distilled water can be substituted for a drug, and the same result obtained, even including the relief of pain.

## *The balance sheet of successes and failures*

When a new drug has passed all the tests of its activity and its relative non-toxicity, and when it has been given its name, which usually conforms to the international nomenclature approved by the World Health Organization, it sets out on its journey through the world.

Improvement in health in many countries has undoubtedly resulted from the astonishing progress made by therapeutic substances in recent years. People nowadays seldom die of typhoid, and hardly do so any more from other infectious diseases; diphtheria, once the terror of all mothers, has practically disappeared; the ravages of tuberculosis too have diminished, especially in young persons. People everywhere live longer and infantile mortality has decreased.

Cruel facts oblige us, however, to recognize that many diseases are still without real drug treatment; cancer, for instance, and many cardiovascular affections. We still need other methods and especially new drugs for treating these diseases. Paradoxically, it could almost be said that we have too few and at the same time too many drugs, for besides the discoveries made by successful research workers and the existence of natural sources, the invention of new drugs has become the business of the large pharmaceutical industry.

Among all the products that come from chemical laboratories—the productive capacity of which exceeds that of physiological and clinical laboratories put together—it may be asked how many will become real drugs with a guaranteed action and a constant effect. Pessimists say 1 in 1,000, optimists 3 or 5 in 1,000, at the most. It may also be asked what other industry could survive such a return on investment. In the drug industry, one real success pays for everything, for the enormous cost of research, as well as for the manufacture and launching of the product. But these costs must be quickly recovered, and this explains the high price of some drugs, especially during the first weeks of their existence.

How long will this kind of success last? The question cannot be answered with certainty. Some proved drugs remain popular with doctors and the public for years. During 1960, the manufacture of aspirin in the United States reached 9,000 tons (28 thousand million tablets). Aspirin is said, with good reason, to cause gastric ulcers and cardiac asthma, but its reputation is exceptionally constant and long-lasting. On the other hand, how many drugs are there which were considered indispensable a few years ago and have now disappeared? In many cases the curves of consumption of new drugs often fall rapidly and sometimes vertically. What are the reasons for this? Some may be inherent in the drug itself. Perhaps certain undesirable secondary effects may appear, over which a discreet veil had been thrown to begin with. Other products progressively lose their activity in the body, which sets up a defence against the aggressor and renders it ineffective. It is well known that some antibiotics quickly create races of micro-organisms which are resistant to their action and even create resistance to the action of antibiotics belonging to related groups (cross-resistance). This resistance can be overcome only by appropriate combinations of antibiotics such as those that are used today, notably in the treatment of tuberculosis.

We must not forget that the patient—or his relatives and friends—exercise an influence that is sometimes predominant on the life or survival of a drug. There are some fashionable drugs which it is generally agreed are of great benefit. Those who consult a doctor, however well-informed they may be, may find it surprising when he does not prescribe them.[4]

The progress of pharmacology as a science of drugs will continue to take a favourable course only so long as man is well aware of the qualities and defects of that marvellous and ubiquitous servant, the drug, to which we owe the prevention or cure of so many diseases, the protection of our cradles and the suppression of pain. But man must not become its slave. He must learn to realize that it has drawbacks as well as advantages. Only then will he be able to make full use of the precious resources that it offers to him.

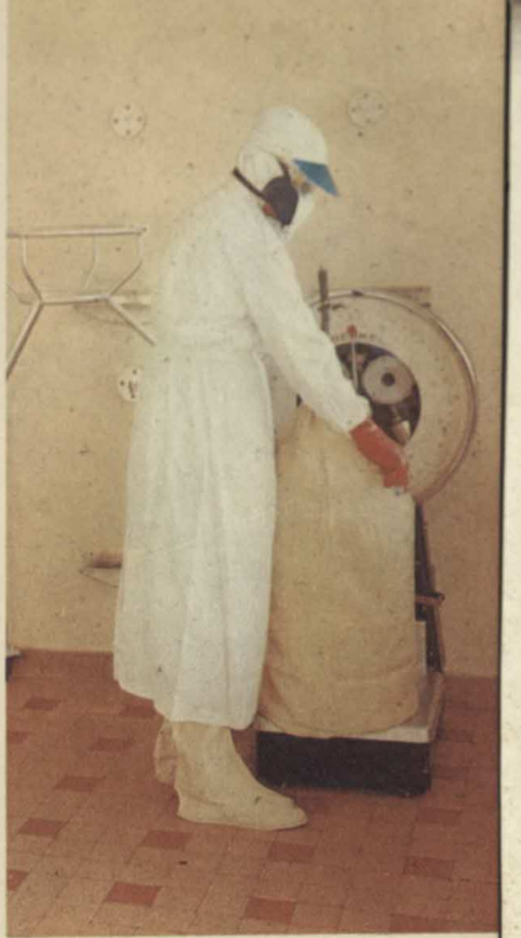

*Fig. 2. The preparation of bipenicillin in a sterile room. Here the antibiotic is being weighed. Note the sterile clothing similar to that of a surgeon, overall, mask, cap, gloves and boots. (Photo by the Société Parisienne d'Expansion Chimique, Maisons-Alfort, Seine).*

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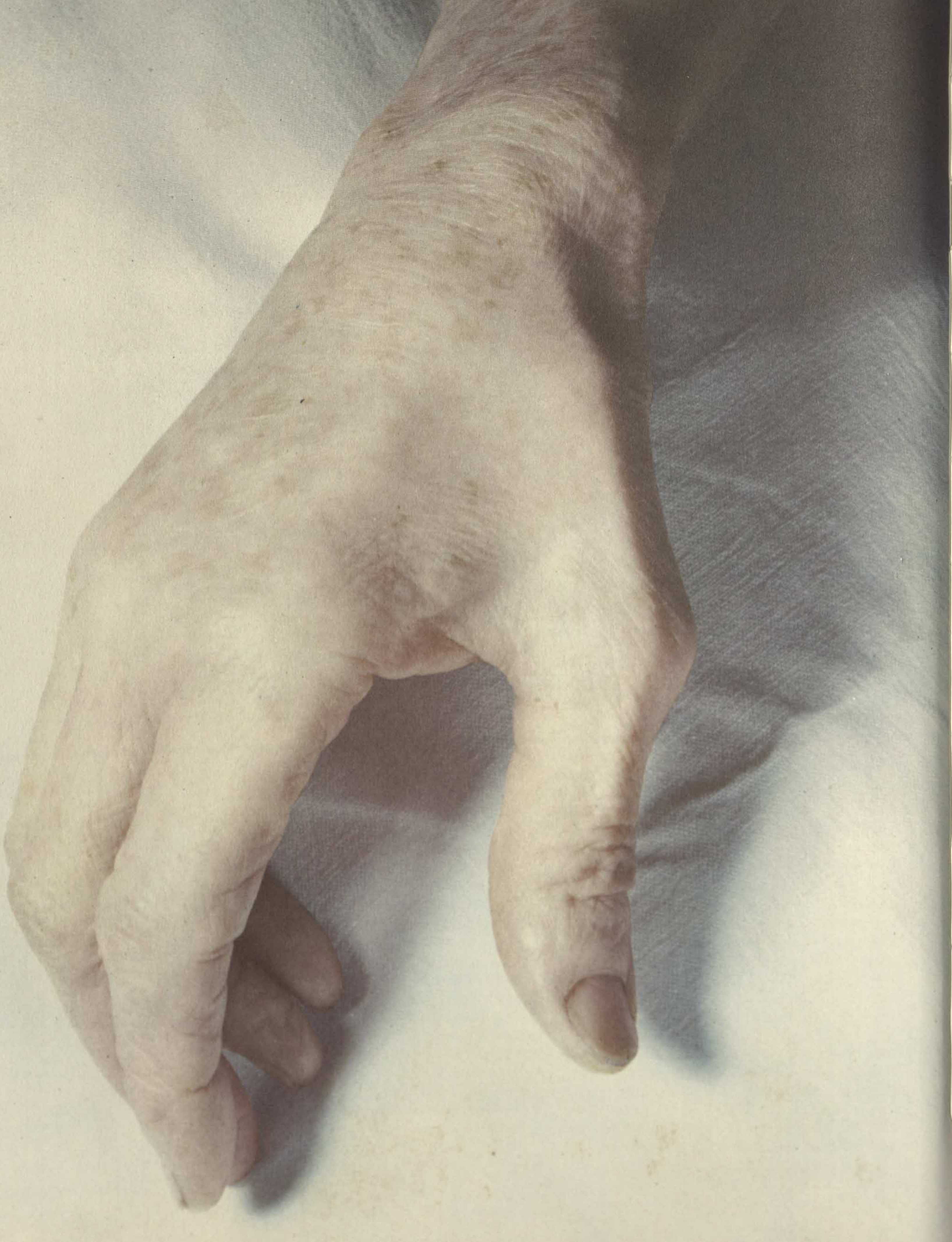
(4) *Here we touch on a real evil of our age: self-medication. People who believe themselves ill or simply off-colour, physically or mentally, often use wonder-working drugs or pills to make themselves happy or successful. Tranquillizers, to speak only of these, although undoubtedly beneficial when appropriately prescribed, bring danger to millions who consume them without prescription. By taking them to rid themselves of their various worries, these people risk falling into a physical and mental state which makes them incapable of any kind of physical or mental effort. The danger is serious and extensive: in the United States alone it is said that 450 tons of tranquillizers are consumed each year.*



# Meditations of a convalescent

Georges DUHAMEL

*I had been expecting this illness for some months, but I did not fear it. I believed that only an acute crisis could resolve the problem of my health and, indeed, of my whole life. Daily recurring ailments, sleepless nights not without pain; I endured the ills, sometimes slight, sometimes serious, that flesh is heir to, the poorliness that affects man's mental balance, suffering that threatened my sanity. I felt sure that this suffering, though varying in its intensity, could only end in a violent rebellion against the exhaustion and humiliation to which my wretched body was being subjected.*

I did not dread such a rebellion. I would have welcomed it; I longed for it during my sleepless nights, burdened with gloomy thoughts. To add to my distress, my body responded perversely and mutinously to the care that I lavished upon it in my anxiety to placate it. The tablets I swallowed every night only made me want to sleep the following morning, when a new day had begun with all its demands and duties. I coaxed my appetite with suitable drugs, but it would only be stimulated by the caprice of days of hard work. I, who had so enthusiastically travelled the world, now trembled at the mere thought of making even the shortest trip involving no mental or physical strain whatever. The smile that formerly lit up my face and the lines on it, was it going to be replaced by an expression of bitterness and despondency? This was the sort of thing I asked myself twenty times a day. Then I thought that if the crisis failed to provide a radical solution, I should be glad to die. I perceived an anxiety equal to my own in those nearest to me and in my friends, and even the sunlight at the best hours of the season failed to comfort me; instead it seemed to threaten and challenge me.

When the crisis came at last, it was in the most unexpected way, which astonished and disconcerted me. One night, I lay visualizing the tortures inflicted on me, I called upon them to declare themselves one by one, I compared them, classified them, and defied them in the silence of the night. I saw them as people, as evil spirits, and I challenged them to do their worst and as suddenly beseeched them to be gone. That same night, I suddenly realized that I was going to experience a nightmare, and that, however distressing it might be, sleep was about to overtake me.

I have had many nightmares during my life, but they have rarely left any clearly-defined memory. If I try to recapture them I feel stifled by an oppressiveness against which I am powerless to struggle; because I do not possess those remedies or drugs that are usually within the reach of others like myself.

That night, the night of my body's rebellion with its unforeseen consequences, I suddenly found the courage to get up in order to escape the growls of the tragedy taking place within me. At all costs I had to get up and walk about a little, in an attempt to regain the salvation of wakefulness.

But the nightmare would not set me free or release its grip upon my mind and body. I walked about in the darkness like a lost soul. Then I stumbled against a bookcase. The impact was not sufficiently painful to shock me back into awareness and the nightmare still possessed me. It made me turn round, go back into bed and pull the bedclothes over me again.

Was I about to sink down into longed-for rest? Or would I wake up and once again begin to analyze and enumerate all the pains which provide the weird and frenzied accompaniment to the life of a rheumatic, an arthritic . . . an 'algetic', as I have thought fit to call myself?

It is difficult to believe that the nightmare must have lasted at least a fortnight. Did I eat? Did I drink? Did I speak? Did I have the strength to complain? I cannot be sure. Sometimes I had the feeling that several people were whispering round my bed. Sometimes one of them would take my hand and feel my pulse. I was told afterwards that once I spoke and gave my opinion on an urgent family problem. I have not the slightest recollection of this.

Sometimes the nightmare, without releasing its grip on me, would recede. With sudden awareness I touched my painful joints and—such is the force of habit—I murmured a diagnosis. Whether I actually spoke the words or not, I certainly thought: Tophus. Tophus. Uricaemia . . . Yes . . . Uricaemia! This prognosis on the future of my wretched body filled me with compassion.

Then suddenly one morning, after two weeks of this strange withdrawal, I regained complete consciousness, as if I had woken after a good, healthy night's sleep. I realized that my life had been saved, that the terrible illness was slackening its hold. But my mind reviewed the thousand problems that I would have to face: the enormous quantity of correspondence I would have to read; the fact that I would have to come to terms again with a world, not cruel but indifferent to me and my troubles.

These problems made me uneasy, anxious, and even afraid. I knew enough about life to think that it can be treacherous. First of all, as I understood that I was going to become convalescent, I did not know what to expect from my weakened body.

I had not been attacked by other living beings; nor had I been attacked by a microbe disease; no external factor was responsible for my illness. The complaint from which I had suffered, and from which I continued to suffer, could clearly be attributed to faulty functioning of the organs and tissues of my own body. I myself was producing those toxic substances which in healthy people are extracted from the blood by the kidneys and eliminated. My body, however, was unable to eliminate its own poisons. I was what I have on occasion called an 'algetic': what doctors describe as an arthritic.

During the course of my life I have experienced arthritis in nearly all its forms: the excruciating pangs of rheumatoid-arthritis (without heart-failure, however, for even in misfortune there can be unpredictable luck)—violent sciatic pains, arthro-cervico brachial

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neuritis, arthroses—in short, I have run the whole gamut of pain. If I went to hot climates, which was sometimes essential, I almost always suffered from attacks of renal colic, since the excess uric acid in my body had to be eliminated somehow.

I wondered if I was to blame, if perhaps my diet or standards of hygiene were inadequate. This is surely one of the questions which convalescents ask themselves, though in my case the answer was 'no'. Normally I ate and drank very little. I resolved to become even more abstemious, and never to eat or drink anything which would aggravate my suffering.

I touched with my fingers those joints of my body that I could reach. I recognized my deformities with some bitterness. What would old age do to me? And what could my spirit do to rise triumphantly above the suffering of a body that might soon be useless?

Let me say here and now that I was not crushed by these thoughts. I wanted to live, and to fulfil all my obligations. I was the head of a splendid and numerous family. My children and grandchildren came to see me several times a day after I regained consciousness and when I could once more take delight in listening to them.

For I was proud of them, and the thought that they might inherit the arthritis from which I had suffered and was still suffering so cruelly, disturbed me deeply. However, it would be up to me to set an example to my children and grandchildren. They must learn how to look after themselves, to forestall the disease, and to take the thermal cure that I myself had always hoped to do but for which there had been no time in an overcrowded life.

Having reached this point in my thoughts, I finally resolved to follow the prescribed cure. I would go to some spa; I would drink what I was told to drink; I would take the baths when I was told to take them. Did this mean that I should have to rest completely? This was no simple question. I am one of those people who have worked very hard all their lives and who therefore no longer know how to relax. Normally, I work all day. At night, as I wait for sleep, which I can never be sure will come, I ask myself a certain question which is both a prayer and an interrogation: 'Have you, today, learned, understood or accomplished anything? If you have, then you can attempt to go to sleep.' This brief soliloquy proves that, paradoxically, work is my method of relaxation. After remembering this, could I just turn over as a convalescent and force myself to go to sleep?

I had dedicated myself to my work. Was I going to forget it even for the time of a dream? Of course not.

At the time of the crisis I had had several books on hand. I dared not put on the light and go tottering and stumbling over to fetch my notebooks and pen. How about starting work again in the secrecy of darkness? I could not do so without risking a severe reprimand. Those who were nursing me had ordered me to relax, and I could not call them and put my case before them, so that they would understand that for me, as I had already stated in one of my books, to work is to relax. No. If I could not be willing, at least I could be dutiful and obedient. All the same, I took a slim notebook and well-sharpened pencil from my bedside table. In the darkness I scribbled down a few thoughts, and as I did so, I felt that my recovery would not be delayed, and that my spirits had in no way been impaired by my body's suffering. I felt that the nightmare had ended, that I could, and must, turn to face life and sing, at least in my heart, a hymn to revival, recovery, and hope.

At last, I left my bed of suffering. My every-day life began again, and I soon realized that it was not going to be easy. Is it possible to ignore a body that has suffered so much? Is it possible to believe that it will immediately regain its full power and flexibility? Is it possible to ignore it even in feeling the simplest joys? Unhappily the answer is

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'no'. The body is there like a witness to our thoughts. We cannot taste even the simplest pleasures without the approval of this physical person which we might think, all in all, was the simple witness to our moral life, our real life.

Matter takes an astonishing revenge: we are constantly reminded of it, and of the fact that without it we could not even pray.

Convalescence of our minds may give us inexpressible illusions, but our bodies remind us harshly that we must think of their convalescence, too, and that this convalescence may well be long delayed. Can men of my age ever forget that illness will leave its mark permanently on their bodies? My soul is rich in memories precious as treasures: meditation enhances them. Our memories can at any time recall sweet music. Does memory itself succumb with our suffering bodies? This is the question we ask all our lives. Can it be that the soul we have so carefully nourished will follow our bodies into decomposition and nothingness?

Whatever anguish the future may bring, I intend to live as best I can. I am deeply moved as I watch my children and grandchildren, my wife, partner of my life, and all those who so devotedly nursed me during my two-months' fight against suffering. I watch them and it seems that I continue to need their help. I am sure that I do. May they guide me, and help me along the path of life and endeavour.

I am going to start my life again. My legs are stiff and painful. Never mind! I am going to walk, climb up and down the stairs which still terrify me. I am going to sit at my desk, fill my pen with ink, start writing, and handle my books, which I must now regard as precious and essential burdens.

Tomorrow I shall go out. Yes, I shall leave the room where I have suffered so much. I shall mingle with people in the streets, then I shall visit my colleagues and friends, all those who for the past two months have thought of me as doomed. I am going to live my life bravely and, who knows?—perhaps joyfully. This will probably be the surest method of restoring flexibility and vigour to my poor body.

I shall come home in the evening, secretly proud of my courage. I shall read my correspondence and all the daily papers. Then I shall go to bed, carefully concealing my delight.

But torments will still await me as I pull the bedclothes over me; the pains are there and I shall still suffer during the long winter nights.

I certainly am a convalescent. Many of my friends regard me as one raised from the dead, and I know that much suffering will still be my lot.

I long for the summer with its light, warmth, and glorious sunshine. I wonder if I shall still be only a convalescent when the time comes to walk among the flowers and trees. Will the suppleness of my joints be restored to me one day? I want to believe it, and minute by minute I marshal my thoughts against the powers of darkness and doubt.

I am not a submissive invalid, crushed and already branded by illness. In my solitude what I whisper is perhaps a prayer, a prayer to the forces of life and joy.

* * *

Duhamel

# In favour of a humane medicine

*Raoul KOURILSKY*

*At the beginning of the twentieth century, medicine took a decisive step forward; it joined biology in systematic research into the causes of diseases and how they operated. The enormous potential of the biological sciences has now been turned towards the investigation of disorders.*

But the complexity of modern medicine escapes most of us. Immediate and empirical solutions are demanded of the hard-pressed doctor going from one patient to another and from one problem to the next. What the modern doctor needs is time to reflect, time to keep up with all that is new in medicine, and not least, to give each patient psychological support. This is the disinterested aim of universities and scientists, but how can it be achieved in the immense complexity of a modern society? On his own, pulled this way and that by the contradictory demands of modern life, the doctor is no longer the master of his own destiny. Herein lies the whole problem. Some doctors are able to solve it by full-time work in specialized fields, but this applies only to a very few and is not a panacea. Much time will be needed, much thought and co-operation, before medicine, and the doctor, achieve the position that they should occupy in society to be of the greatest benefit to us all.

The biologist is no longer ashamed of medicine, which he used to consider as outside science. Even when he sets himself to elucidate fundamental problems, he thinks of medicine; he no longer hesitates to seek confirmations, analogies and ideas in medicine; he no longer immures himself in 'pure biology'.

Conversely, the appeal of biology has been heard by the medical world: an increasing number of doctors have become scientists and now work side by side with biologists to discover the secrets of living matter and the mystery of its disorders.

The arsenal of the sciences has been placed at the service of disease. The examples that have been given in this volume afford a measure of the knowledge that has been extracted in a comparatively short time from nature. This is not by any means a complete account, however, of all aspects of this knowledge, for there are many subjects which it has been impossible to deal with. But the aim was not to write a treatise on medicine.

There are no longer any limits to scientific investigation; no sphere or form of research is forbidden and none is impossible. Biology indicates the bases and the points of departure. Thereafter, unceasing research leads on towards discoveries that are always possible, though never certain. And, on the way, nature uncovers herself; the little that one can learn from her is always useful to medicine, for in nature there is no deception.

Everything is now the object of research: the body and its mechanisms, the environment and its properties, the inheritance of organisms. Investigations into all of these were formerly fragmentary and isolated: now they are co-ordinated. Relationships and correlations present themselves increasingly to the mind of the research worker. The sciences, have become interdependent.

In earlier times the research worker was the craftsman of his own research. Today a whole team of workers has to direct a series of different disciplines on the same objective, each strictly appropriate to the common theme of their research. This immense effort will go on unceasingly, amplifying itself as it does so, and at the same time raising vital problems of national and international co-ordination. Throughout the world each worker recognizes those working on the same theme and in the same spirit, and he must be ready to collaborate with scientists who work in spheres other than his own.

In spite, however, of this vast expansion of scientific activity, some of man's most formidable scourges still retain their secrets; nor will these be disclosed merely by chance: discovery will spring from the enormous total of the world's researches as a chain reaction.

But what becomes of human medicine, which everyone desires and yet at the same time fears, knowing that sooner or later disease will enter into his life?

Medicine is widely criticized and harsh judgments are delivered about it. Some wish to make quicker changes, to reduce the importance of therapeutic treatment because of the progress of preventive medicine and the conditioning of man; others are so attached to the simple medicine of the past that they fear all modern innovations.

The troubles of modern medicine often arise from the increasing difficulty of having to treat serious cases elsewhere than in a large hospital, and also from the impossibility of diagnosing many diseases without relying on numerous and repeated biological controls.

These necessities make themselves felt at a time when the psychological relationship between doctor and patient must be deeper and more understanding than it has ever been; not only because the doctor's duty is to guide his fellow men through the complicated processes of diagnosis and treatment, but also because it is nowadays realized that improved conditions in the affective sphere, if planned and carried out with the help of the patient himself, will be of decisive importance in helping to free him from many of his ills.

Human activity has resolved many abstruse problems; why should this one be insurmountable? The direction in which medicine is evolving is clear; better medical training must be instituted to keep pace with the growth of human knowledge; conditions must be established for the doctor so that his fullest personal capacities can be deployed for the benefit of the patient

Far from stifling individual medicine, science must, on the contrary, contribute to its transformation so as to secure greater efficiency. The ideal would be for each doctor to be not only a scientist but also a psychologist, so that treatment would be appropriate, errors of diagnosis limited, expenditure reduced, and complications prevented by being foreseen. There is no reason to think that a doctor can solve the innumerable questions that arise over each patient without devoting, not the minimum but the maximum of time and patience, just as the solution of the smallest experimental problem requires it. It is, in fact, more difficult to reconstruct the unknown conditions of the natural experiment that constitutes a disease than to control the consequences of an experiment which has been planned by the scientist himself.

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